CHARACTERIZATION OF THE CANINE GASTRIC EMPTYING OF AND THE GASTROINTESTINAL MOTOR RESPONSES TO HYDROPHILIC POLYMERS

BY

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CHARACTERIZATION OF THE CANINE GASTRIC EMPTYING OF AND THE GASTROINTESTINAL MOTOR RESPONSES TO HYDROPHILIC POLYMERS

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(Under the supervision of Professor Paul Bass)

Hydrophilic polymers include bulk laxatives, many of which are dietary fibers. The aims of the present investigations were: 1) to characterize the canine gastric emptying patterns of, and the antroduodenal motor responses to meals of increasing hydrophilic polymer content; 2) to examine whether the gastric emptying of polycarbophil (PC), an indigestible particulate gel, was dependent on interdigestive motor activity (phase 3); and 3) to characterize the jejunal motor responses to laxative and non-laxative hydrophilic polymers. Guar, pectin and psyllium meals presented as homogeneous gels while PC meals were particle-liquid mixtures. Pectin, psyllium and guar exhibited concentration-dependent increases in viscosity and nonNewtonian flow patterns.

Half-emptying times ($E^{1}/_{2}$) of 300 ml test meals were determined in dogs with duodenal cannulas (psyllium and guar meals) and gastric cannulas (PC meals). The antroduodenal contractile responses to polymer test meals were monitored using serosal force transducers. In addition to antroduodenal responses, the jejunal motor responses to laxative (psyllium, PC) and nonlaxative (pectin) polymers were characterized.

As meal polymer content increased, meal $E^{1}/_{2}$ increased. High polymer content meals of psyllium (3%), guar (1.5%) and PC (90 gm)

exhibited $E^{1}/_{2}$ of 40, 34 and 300 min, respectively. None of the test meals elicited significant antroduodenal motor activity. Importantly, 50% of the 90 gm PC meal emptied in the absence of phase 3 activity. Bulk laxative polymers did not uniformly affect jejunal motility. Instead, the homogeneous gels of psyllium and guar concentration-dependently increased motor activity and delayed phase 3 activity. No patterns of contractions were seen. In contrast, PC did not increase motor activity but converted control-level activity into propagated groups of contractions. PC did not delay jejunal phase 3 activity.

We conclude: 1) meal viscosity, but not antroduodenal motility, influences the gastric emptying of viscous polymer meals. However, the nonNewtonian character of the meals precludes a strict relation between meal viscosity and motor activity or emptying time; 2) the phase 3-independent emptying of PC argues against the traditionally held requirement of phase 3 activity for the emptying of all indigestible ingesta; and 3) bulk laxative polymers do not uniformly affect jejunal motility. Instead, the physical form of the meal substance probably influences the character of the motor response.

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Preface:

This thesis is presented in five chapters. An introduction is followed by four research reports. The introductory chapter contains broad reviews of gut motility and the regulation of gastric emptying. These reviews provide terminology and background physiology which complements the research reports. A discussion of hydrophilic polymers and their effects on gastric emptying and gut motor activity follows. Finally, unanswered questions concerning the effects of hydrophilic polymers on gut function are ennumerated. These questions are then addressed in the research reports.

Chapter One

Introduction

I. GASTRIC AND INTESTINAL MOTOR ACTIVITY OF THE UNANESTHETIZED DOG

Patterns of gastric and intestinal motor activity - Gastric and small intestinal muscle each exhibit distinctive motor patterns in the fasted state. After feeding, the fasted state patterns are replaced with a typical post prandial pattern of contractions. As the meal empties from the stomach, the postprandial motor pattern begins to wane and the fasted state patterns begin to reappear. Dogs and man exhibit qualitatively similar patterns of gut motor activity. Thus the dog has been employed for investigations pertinent to how the human gut functions.

Fasted state motor activity has 3 principle features: 1) motor activity presents in a unified pattern with the whole pattern repeating, i.e., exhibiting a periodicity, 2) this motility pattern is comprised of 3 major levels of contractile activity, and 3) one of the activity levels, presenting as a brief period of maximal amplitude contractions, migrates from the stomach to the ileum at regular intervals. These 3 main features of canine motility were established throughout the period 1911-1969.

Fasted state contractile activity is periodic in its appearance. As early as 1911, Boldyreff demonstrated that a brief interval of contractions appeared on the stomach every 75 to 90 minutes (1, review see 2). Throughout the first part of the twentieth century, allusions to this periodic event appeared in the literature (3,4), but its significance was not speculated upon. In 1967, Reinke et al. (5) confirmed Boldyreff's observations on gastric motor periodicity and showed that small intestinal activity was also periodic. Based on the observation that these periodic episodes of gastric contractions delivered gastric secretions to the duodenum, Reinke postulated that this activity acted to cleanse the stomach and small intestine of cellular debris, and secretions (5). Subsequently, the presence of intestinal periodic activity was confirmed and extended by others (6,7,8).

Periodically recurring contractions are only part of the overall fasted state motor pattern. This concept was originally advanced by Boldyreff (1). However, he did not characterize the temporal distribution of contractions of the fasted state. From 1911 until 1967 there appeared numerous reports on the many varieties of contractions seen in the fasted

state, but exactly how such activity fit into a coherent pattern was not detailed (9-11). In retrospect, pattern recognition was delayed because motility studies had traditionally been performed using anesthetized dogs, intraluminal sensors, and by studying only brief periods of motility. It was not until chronically implanted extraluminal contraction sensing units were coupled with long recording times that the patterns of interdigestive activity were recognized.

In 1963, Jacoby et al. (12), and shortly later Reinke et al. (5) described 3 major patterns of contractions - basal, preburst and burst - which comprised the fasted state contractile pattern. The basal state lasted about 40 minutes and was associated with few contractions; the preburst state lasted about 9 minutes and was associated with contractions of intermediate amplitude and frequency; the burst state lasted about 10 minutes and was marked by contractions of both maximal amplitude and frequency. The terms basal, preburst and burst were descriptive, and their serial appearance gave order to the analogous type 1, 2, and 3 contractions first described by Carlson in 1913 (13). To date, a variety of workers have

confirmed and expanded the description of the phases of periodic interdigestive motor activity (6,7,8,14).

Gastric and small intestinal periodic motor activity migrates in an aborad direction. This third major characteristic of fasted state motility, the migrating myoelectric complex, was documented in 1969 by Szurszewski (6). Using serosal electrodes and long recording sessions he recorded the myoelectric correlate to the basal, preburst, and burst intervals described by Reinke et al.(5). However, Szurszewski demonstrated that the burst or "electric complex" first appeared in the duodenum, and then appeared at caudally situated recording sites as far as the terminal ileum. As one complex finished in the ileum, another appeared in the duodenum. Since this first description of the migrating myoelectric complex, other workers have demonstrated that the complex starts in the esophagus (15), migrates through the stomach (8) and terminates at the ileocecal junction (16,17). Functionally, the migrating complex appears to periodically sweep cellular debris secretions and indigestible meal residues from the stomach and small intestine. Such a sweeping action has been documented cineradiographically (18,19).

After a meal, fasted state gut motor activity changes. The distinctive periodic activity is replaced with a continuum of contractions of intermediate amplitude and frequency. Gastric and duodenal contractions are coordinated to facilitate gastric emptying. As the meal finishes emptying from the stomach, the fasted state motor patterns are gradually reestablished. The character of the fed state motor pattern is described more fully elsewhere (vide infra, pp.25)

Control of gastrointestinal motor activity - Various workers, notably Cannon (9), appreciated that the stomach and small intestine could contract at different rates. Control of the frequencies of gastric and intestinal contractions is still incompletely understood. However, observations of gut myoelectric activity, recorded with extracellular electrodes, have clarified certain elements of this control (20). Note that electrodes detect membrane potential changes, not contractions. However, certain electric events do correlate directly with contractions (vide infra).

Gut muscle exhibits omnipresent cell membrane potential changes first described by Alvarez in 1922 as

"action currents" (21). This myoelectric event recurs with a fixed rhythm, is electric in nature and sets the maximum rate at which contractions of the circular muscle may occur. Therefore this membrane change has been termed the basic electric rhythm (BER) (22). Various other descriptive synonyms have also been employed (slow waves, pacesetter potentials, electric control activity, review see 2).

Until recently, the BER were thought to originate in the longitudinal muscle layer and spread electrotonically to and be amplified by the circular muscle layer. Currently, attention is being focused on a requirement for the interstitial cells of Cajal. These cells are distributed throughout the major intestinal plexuses (24). Prosser has recently demonstrated that selective destruction of the cells of Cajal results in the abolishment of the BER in longitudinal and circular muscle strips (C.L. Prosser, personal communication). In addition, Fox et al. (25) have recently demonstrated that selective damage of the myenteric plexus ganglia also disrupts the appearance of the BER <u>in vivo</u>. Whether the cells of Cajal are the source of the BER awaits characterization of their electric properties and their relation to surrounding

cells.

The BER frequency is established by pacemakers located in the orad gastric corpus (26) and the orad duodenum (27). Whether pacemakers are single or grouped cells is uncertain. Pacemakers exhibit higher rates of spontaneous depolarization than neighboring cells. Neighboring cells are thus entrained to the higher frequency (28). A brief but significant amount of time (phase lag) is required for the entrainment of neighboring cells. Thus the gastric and duodenal BER appear to be propagated aborally from their respective pacemakers. Longitudinal muscle is syncitial, and propagation of BER is evident from examination of myoelectric tracings from closely spaced electrodes. Propagation of the BER may also be demonstrated by artificially pacing the tissue and monitoring BER frequency changes at some distance from the site of stimulus (29).

The gastric BER is paced from the orad corpus at a rate of about 4.5 cpm and the frequency is constant throughout the stomach (26). Similarly, the duodenum is paced from its orad aspect but with a frequency of about 18 cpm (27). In contrast to the stomach, the small intestine displays a gradually decreasing BER

frequency as the ileum is approached. Sarna (28) has proposed that this progressive decrease in BER frequency is due to an electrical uncoupling of entrained cells. Uncoupling may be due to poor intercellular communications. The result is the establishment of a new, lower BER frequency which reflects the inherent rate of depolarization for caudally located bowel segments. Thus the intestinal BER frequency presents as a gradient with the duodenum, mid-jejunum and the terminal ileum paced at about 18, 16, and 14 cpm, respectively.

The frequency of contractions in the stomach and small intestine is determined by the BER frequency (22). Thus the stomach and duodenum exhibit maximal contractile rates of 4.5 and 18 contractions per minute, respectively. The spike potential is the myoelectric correlate of the circular muscle contraction. Spike potentials are superimposed upon the BER in a temporally fixed fashion. Spikes appear just after the potential change that marks the beginning of the BER cycle (22). The BER configuration and frequency is essentially unchanged by food. However, selected drugs such as atropine have been found to increase gastric BER frequency (30). In

contrast to the BER, the appearance and intensity of spike potentials may be influenced by food, drugs, nerves and hormones (31-38).

In contrast to the BER, spike potentials are not propagated (20). However, groups of spike potentials such as those of the migrating myoelectric complex can appear propagated. The aborad migration of the migrating complex is subject to nervous, and hormonal controls (32-35, 37, 38, review see 39).

Technique for recording motor activity from the bowel of the unanesthetized dog - The assessment of gut motor responses has been performed in a variety of ways (historical review see 2). However, experience reveals that both the presence of measuring devices within the bowel lumen (e.g., barium, balloons) and anesthetics (40, 41) can confound the responses of the gut, especially to food. Thus extraluminal sensors for the chronic detection of muscle contractions in the unanesthetized animal were developed.

The strain gage force transducer was introduced for application to gut motility by Jacoby et al. (12) in 1963, and was subsequently refined (5). The unit consists of back-to-back resistor elements combined to

form a half-Wheatstone bridge. During monitoring, a nominal current is passed through the implanted gage. Perturbation of the resistors by muscle contractions alters the flow of current through the gage, relative to a reference half-Wheatstone bridge located in the pen recorder. Thus the muscle contraction is transuced into an electrical signal, which then drives a recording pen.

The methods for the fabrication and implantation of the recording units have been detailed (5,12). In brief, the gages are connected to an electrical connector via 22 inch lead wires. At surgery, the gages and wires are tunneled subcutaneously from the suprascapular region to the flank, caudad to the last rib. The units are passed into the abdominal cavity via a stab wound. The connector plug is implanted subcutaneously in the suprascapular region. The units may be situated in the transverse or longitudinal axis of the bowel. Full thickness ligatures secure the units to the serosal side of the bowel. Recording is performed by connecting the implanted circuit (dog) to the pen recorder via a matching external plug assembly.

Applicaton to present pharmacological investigations -

Procedures for investigating drug actions have been influenced by elucidation of fasted state motility cycles. For example, periods of motor quiescence (phase 1, basal period) are generally used for examination of the contraction-stimulating properties of drugs and meals (5,12). In this way, the presence of spontaneously occurring contractions (seen with phases 2 and 3) do not confound the drug-related responses. Similarly, drugs which inhibit contractions may be administered during the period of maximal motor activity, i.e., phase 3.

Quantitation of contractile responses obtained with strain gage force transducers is conveniently made with reference to some maximal intensity contractile event. Specifically, Code and Schlegel (18,19) have demonstrated radiographically that phase 3 contractions completely occlude the lumen of the antrum and small intestine. As previously described, phase 3 is marked by 5-10 min of contractions which exhibit both maximal frequency and amplitude. Treatment responses may be expressed as a percent of the maximum activity seen during phase 3. This method is particularly useful in cases where the sensitivity of the recording units decreases with time or periodic calibration of the

units is impractical (5).

2. CONTROL OF GASTRIC EMPTYING

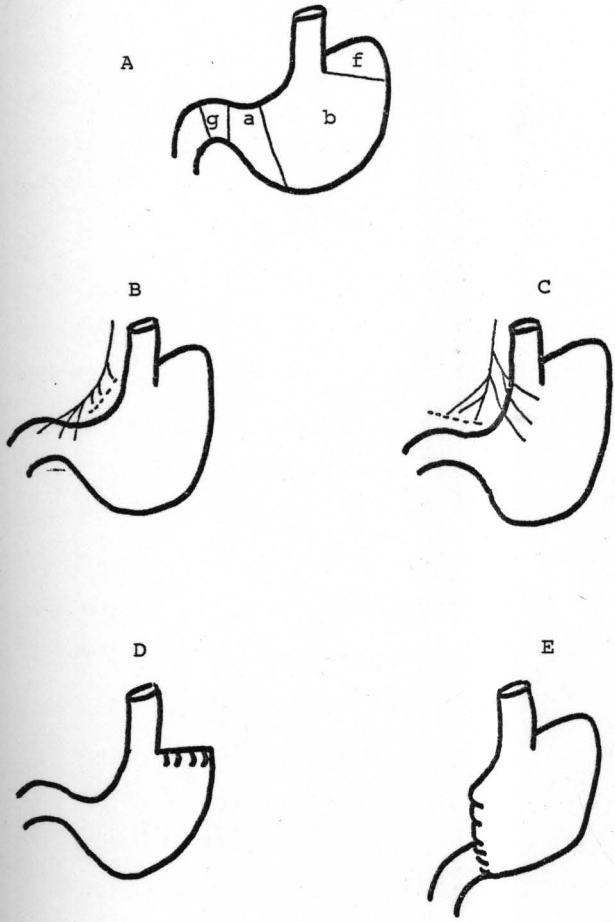
Overview - gastric emptying is the result of cooperative motor responses among the proximal stomach, the distal stomach and the orad small intestine. These 3 compartments each exhibit characteristic motor functions. Nerve and hormonal signals which are tailored to the physical character of the meal determine the magnitude of the postprandial motor response of each compartment.

Current knowledge of how the stomach and small intestine control gastric emptying evolved initially from the surgical treatment of peptic ulcer disease. Therapeutic resection of various gastric and intestinal portions resulted in disturbances of gut motility and emptying (42-44). Subsequently, Cannon's innovative use of x-rays to document the movements of ingesta within the gastrointestinal tract confirmed a role for gastric motility in the preparation of food for gastric emptying (45). Since Cannon's time, the biology and function of the gastric body, antrum and small intestine have been extended. In particular, more

FIGURE 1.

Surgical preparations used to reveal control mechanisms of gastric emptying. A: normal stomach, f-fundus, b-gastric body, a- gastric antrum, g- gastroduodenal junction. B: proximal gastric vagotomy. C: distal gastric vagotomy. D: fundectomy. E: antrectomy.

FIGURE 1.



accurate methods have been developed for the measurement of gastric emptying and the motor activity that influences gastric emptying. The following is a review of the influences of gastrointestinal motor activity and meal physical and chemical characteristics on gastric emptying.

The gastric body - The orad 2/3 of the stomach referred to here as the gastric body includes the gastric fundus and the orad corpus (fig. 1-a). The gastric body acts as a reservoir; it accepts meals of various volumes without significant increases in intragastric pressure. This effect is due to a relaxation of the gastric musculature and may be generally referred to as accommodation. Functionally, accommodation aids in the delivery of food to the orad stomach for trituration (vide infra). Accommodation is also a principle regulator of the gastric emptying of liquids (vide infra). Studies performed as early as 1895 showed that instillation of progressively larger volumes of air or water into the stomach failed, within broad limits, to elevated intragastric pressure (46-48). Gianturco (49) localized accommodation to the orad stomach with radiographic evidence for the postprandial distention

of all or a portion of the orad stomach reduces the accommodative capacity (44,49,50, review see 51).

Accommodation is dependent upon an intact vagal innervation. Truncal or proximal vagotomy (fig. 2b) results in marked increases in intragastric pressure, i.e., loss of accommodation, in response to gastric distention (48, 52). Electric stimulation of the peripheral vagal remnant reestablishes gastric relaxation (53). In contrast to vagal stimulation, stimulation of the sympathetic nerves to the stomach (splanchnic) has quite minor effects on gastric relaxation (53).

The postganglionic mechanism of accommodation is only partially understood. The gastric relaxation produced by electrical stimulation of the vagus nerves is substantially inhibited (ca 80%) by hexamethonium but not atropine or adrenergic blockers (53,54). There is evidence which suggests that a dopaminergic system may be involved. Exogenous dopamine elicits gastric body relaxation in control and vagotomized patients (55), and in dogs (54). This effect is unaltered by pretreatment with propranolol, quanethidine, phenoxybenzamine and dopamine-b-hydroxylase inhibitors (54). However, dopamine-induced accommodation is

completely abolished by pretreatment with dopamine receptor blocking agents such as metoclopramide and domperidone (54,55). A clearer knowledge of the role of dopamine in gastric accommodation awaits characterization of gastric dopaminergic receptors and neurons.

The gastric body is of chief importance to the controlled emptying of liquids. Fundectomy (Fig. 1d), resection of the gastric body, and interruption of the proximal gastric vagus nerves each results in decreased accommodation to meal volumes; the emptying of liquids is hastened (49,50,52,56). In contrast, these procedures do not affect the gastric emptying of solids.

The gastric antrum - The gastric antrum performs an entirely different function than the gastric body. In general, the antrum is a mixing, milling organ. Ingesta is stored in the orad stomach; small portions are pushed into the antrum for milling and fluidization in preparation for gastric emptying. In 1911, Cannon (45) described the mechanical movements of the antrum which he had observed radiographically. The antrum contracts powerfully, and aborally-directed

contractions push portions of ingesta toward the gastroduodenal junction. Each antral contraction greatly elevates intraantral pressure. Only a small fraction of the fluidized digesta escapes to the duodenum. Most of the antral bolus is then retropulsed under pressure into the gastric body to await further mixing. With time, all the food stored in the gastric body is advanced to the antrum for mixing and subsequent emptying.

The magnitude of antral contractions is critically dependent upon intact vagus nerves. Distal gastric vagotomy (Fig. 1c) results in feeble antral contractions which compromise the particle size-reducing power of the antrum (57,58). Under normal circumstances, most particles are of less than 0.2 mm diameter when they empty. After vagotomy, larger particles are allowed to empty (59).

The gastric antrum controls the gastric emptying of solids principally by acting as a sieve. Meyer (59) has demonstrated that after a meat meal, about 90% of all particles emptied to the duodenum are of less than 0.2 mm diameter, and 99% are of less than 2 mm diameter (59). After antrectomy (Fig. 1e), the sieving capacity of the stomach is significantly reduced but not

of the stomach is significantly reduced but not abolished. Thus, antral mixing alone does not fully account for the particle size reduction. Peptic digestion and simple dissolution also participate.

Antral sieving is more dramatically, albeit less physiologically, demonstrated by the gastric emptying of large (7mm diameter) plastic spheres. The gastric antrum prevents spheres from emptying from the stomach until after all other ingesta is emptied (60). As interdigestive patterns are reestablished, spheres are swept from the stomach by phase 3 contractile activity (57,58). After antrectomy (Fig. 1e), sieving is lost and the spheres empty prematurely into the duodenum pushed by weak, arrhythmic contractions of the gastric remnant. After antrectomy, the loss of sieving is reflected by the increased particle size of conventional foods which are allowed to empty (57-59).

In contrast to the gastric body, the gastric antrum plays little part in the emptying of liquids. Neither distal gastric vagotomy (Fig. 1c) nor antrectomy (Fig. 1e) affect the gastric emptying of liquid test meals (5,7,58,60).

The orad and caudad parts of the stomach cooperate to effect gastric emptying. The gastric body and

of liquids and solids, respectively (51). A general pattern of gastric emptying exists. Liquids empty more rapidly than digestible solids, which in turn empty more rapidly than indigestible solids. Although the gastric emptying patterns for a variety of liquids and solids have been reported, the gastric emptying of indigestible solids has not been adequately studied. Indigestible solids refers to meal residues which are not degraded by peptic digestion and are generally of large particle size. These residues include dietary fibers (vide infra). To date the gastric emptying of large indigestible spheres has been accepted as a model for the gastric emptying of indigestible ingesta. New information concerning the gastric emptying of indigestible material is presented in Chapter 3 (vide infra).

The gastroduodenal junction - The gastric antrum is interfaced with the duodenum. This anatomical region is called the gastroduodenal junction, pylorus or pyloric sphincter. The circularly oriented band of muscle which demarcates this area is a thickened portion of antral circular muscle (61). Because it represents a narrowed passage between the stomach and

duodenum, anatomists and physiologists previously ascribed to it a role in gastric emptying (45). To date, evidence has accumulated which does not support a role for the gastroduodenal junction in the control of the gastric emptying of liquids or solids.

Enlargement of the gastroduodenal junction does not alter the emptying rate of liquids. Neither implantation of a noncompressible tube to prop open the passage nor surgical enlargement of the gastroduodenal junction by pyloroplasty alter liquid emptying (62-66). Although the gastroduodenal junction does not appear to influence liquid emptying, it does act to prevent duodenogastric reflux. Dogs with circumferential pyloric myomectomy exhibit a significant reflux of radiolabeled duodenal perfusate into the stomach over the course of a test meal (67). Duoenogastric reflux of bile is a recognized cause of gastric ulcer.

The gastric emptying of solids is minimally affected by pyloroplasty (65,59). Pyloroplasty does slightly impair the milling action of the antral contractions. After pyloroplasty a slightly greater percentage of food particles emptied exceeds the usual 0.2 mm diameter limit (59).

Gastroduodenal pressure gradients and gastric emptying - The stomach does not exert exclusive control over gastric emptying. The stomach is situated in series with the duodenum; the pyloric canal connects the 2 compartments. The ability of antral contractions to elevate terminal antral intraluminal pressure has been described. The orad duodenum, or any closed section of the bowel, may also exhibit intraluminal pressure changes. The tendency for gut content to travel from the stomach to the duodenum is idealized according to the law of Poiseuille:

$$\frac{P_g - P_d}{R} = \frac{dv}{dt}$$

Where P_g and P_d represent the intraluminal pressures of the stomach and duodenum, respectively; R is the resistance to flow caused by the pyloric canal; dv/dt is the change in gastric volume with time (68). Naturally, the flow rate will be affected by the nature of the fluid leaving the stomach. Test meal chemical (e.g. fatty acid content) characteristics can affect gastroduodenal motor activity and thus influence pressure gradients (vide infra). Such changes can be

hormonally or neurally mediated (vide infra). The modelling of the gastric emptying process is not considered here. Instead, the effects of test meal components on the rate of gastric emptying, and how such rate changes are effected will be reviewed to provide an estimate of how the stomach and small intestine jointly contribute to the control of gastric emptying.

Antroduodenal contractile responses to food - Meals elicit antral and duodenal contractions which, with gastric body tonal changes, execute gastric emptying. After a meal, the antrum and duodenum contract at about 75 and 50% maximum frequency, respectively (69,70). The duodenal contractions are temporally coordinated with the antral contractions (69,71,72). Radiographic correlates of postprandial contractions confirm a role for coordinated antroduodenal activity in the control of gastric emptying. Briefly, an antral contraction pushes a small portion of fluidized ingesta through the pyloric canal. The terminal portion of the antrum contracts after which the duodenum contracts once or twice. Temporally, the pyloric canal was closed before the antrum completed its contraction. Therefore antral

intraluminal pressure increased and caused retropulsion of the remaining fluid back into the gastric body. The duodenal contractions propelled the emptied portions of fluid aborally, prevented duodenogastric reflux, and prevented further emptying of the meal. Since gastric antral BER frequency is about 4.5 cpm, this coordinated antroduodenal sequence also occurs about 4.5 times per minute. As the period of postprandial gastric emptying ends, the fed state pattern wanes and is replaced with the interdigestive periodic activity.

The coordination of postprandial antroduodenal motor activity is dependent upon an intact enteric nervous system since gastroduodenal junction transection and reanastomosis abolishes postprandial coordination (73). In contrast, extrinsic nerves may not be required since vagotomy has no disruptive effect (74). However, the effects of sympathectomy have not been studied. While the postprandial pattern is most evident after meals of solid rather than liquid food, the physical presence of food is not an absolute requirement. Diversion of the antrum and orad duodenum from the digestive path does not prevent the postprandial appearance of the coordinated pattern (75).

(75).

Control of gastric emptying as revealed by liquid test meals - Liquids empty more rapidly from the stomach than solids, and nearly all digesta presented to the intestine is liquified. Therefore liquid meals have been employed for the study of the controls of gastric emptying. Since dietary fats, carbohydrates and proteins can be solubilized, their respective addition to a standard test meal reveals how each meal component may affect gastric emptying. To date, the effects of meal volume, osmolarity, pH, fatty acid content and overall caloric density on gastric emptying rate have each been investigated. Most work has been performed in humans (review see 99). Results in dogs, where available, are qualitatively similar and confirm the utility of the canine model for studies of gastric emptying.

Pattern of liquid emptying - The gastric emptying of liquids may be quantified by performing serial collections of gastric effluent from a duodenal cannula. More commonly, liquid meals are administered and after variable amounts of time, the meal fraction

remaining in the stomach is determined by aspiration. (the serial test meal procedure). Gastric emptying is commonly depicted with a plot of the meal fraction emptied (or recovered) vs time. The gastric emptying of liquids follows a log-linear pattern reasonably well (100). However, exponential emptying is most clearly evident over the mid-portion of a typical cumulative % recovered vs. time curve. The initial portion of the curve usually reveals faster or slower emptying with meals of larger (e.g. 1200 ml) and smaller volumes (e.g. 200 ml), respectively. Completion of emptying is usually protracted, relative to the first 60-80% of the meal (100,101). The general exponential appearance of the mid-portion of the emptying curve persists irrespective of meal volumes tested (range: 100-1000 ml).

Estimates of gastric emptying rate are, by convention, reported as the meal half-life, or more accurately, half-emptying time (E 1/2) (100). However, an E 1/2 does not describe the completeness of emptying or the initial and final patterns of emptying. Thus, untransformed emptying curves and emptying rate constants (slopes of least squares plots) for each portion of the curve, are currently being advocated as

The liquid test meal represents a simplified case. Meals are commonly comprised of liquid and digestible solid. The liquid portions empty first. The digestible solids undergo liquification to chyme prior to emptying. Thus while solid food does empty ultimately as a liquid, it does so slowly, demonstrating a pattern akin to a zero-order process (59,102). Evaluation of the slowing effects of individual meal components on gastric emptying is easiest with otherwise rapidly emptying liquid meals.

As meal volume increases, the E 1/2 increases (101). This effect is seen over a wide range of meal volumes (25-1250 ml) (100,103). The volume effect seen after conventional, nutritive liquid meals reflects a balance between the accommodative powers of the gastric body, and the interaction of the meal components with the orad small intestine. Fat, osmolytes, and other meal substances stimulate intestinal receptors to reflexly slow the rate of gastric emptying (vide infra). The intestine accepts only what it can tolerate.

Gravity principally affects the gastric emptying of rapidly emptying liquids (100). Elevation of the trunk (45 degrees) delays the emptying of isotonic,

buffered liquids but not of hypertonic glucose meals (stimulant vs nonstimulant liquids, vide infra). Considering the usual postprandial posture and the stimulant nature of most ingesta, gravity probably is not an important factor in the rate of gastric emptying.

Small intestinal control of gastric emptying - The small intestine contributes greatly to the control of gastric emptying. This is clearly seen in dogs having orad duodenal fistulas. In such dogs, gastric effluent is immediately diverted from the digestive path before contacting the duodenum. In this model, gastric emptying is dramatically hastened. This rapid emptying may be slowed back to normal by reinjecting the gastric effluent back into the small intestine (76,77).

Present understanding of how the intestine influences gastric emptying is derived from testing the effects of various test meal components on the gastric emptying rate of liquids. However, exactly how meal stimulation of the intestine is accomplished and transduced into motor control is only partly understood.

Surgical studies reveal that the antrum is not

critical to the controlled emptying of liquids. However, liquids normally elicit antral contractions which (with gastric body tonal changes) facilitate emptying. Investigations of the role of antroduodenal motility in the control of emptying focus, in part, on this antral activity.

Intestinal control: the enterogastric reflex - Intraduodenal infusions of protein, fat, acid and carbohydrate each results in a rapid reduction of antral contractile activity (78-83, review see 84). This effect is termed the enterogastric reflex (EGR). The reflex is invariably associated with a delayed gastric emptying. Since the reflex is rapid in onset (less than a minute), a neural component has been postulated. However, the ability of test meals to depress contractions in an autotransplanted gastric pouch (totally extrinsically dennervated) suggests that hormones may also participate (85).

Expression of the EGR appears to require an intact postganglionic sympathetic nerve input to the stomach and orad small intestine. Shapiro and Woodward (87), demonstrated that after celiac ganglionectomy, acid no longer elicited the EGR. In contrast, division of the

preganglionic nerves to the celiac plexus (splanchnic nerves), vagotomy, paravertebral sympathectomy, or vagotomy plus paravertebral sympathectomy had no effect on the EGR (81-83, 89). In supplement to Shapiro and Woodward's studies with acid (87) others demonstrated that vagotomy did not alter the ability of intraintestinal fat, acid or carbohydrate to delay gastric emptying (88). Taken together, it is possible that the neural control of the EGR resides solely within nerves which connect the gut with the celiac plexus.

In addition to nerves, the hormones secretin and perhaps cholecystokinin (CCK) may participate in the EGR (review see 90). Secretin and CCK are both synthesized and secreted from endocrine cells located in the mucosa of the small intestine (review see 91). Both hormones are released in response to mucosal contact with products of meal digestion. Gastric acid and bile stimulate secretin release; fatty acids, amino acids and calcium salts stimulate CCK release. Hormonal participation in the EGR is based on motor effects obtained in response to exogenously administered hormones.

Secretin delays gastric emptying in humans (92,93)

and in dogs (94). This effect is due to a relaxation of the gastric body musculature (93,95) combined with a depression of antral contractile activity (94). The effects of CCK on gastric emptying are variable (96,97). In dogs, CCK slows gastric emptying probably by relaxing the gastric body (93,95). The effects of CCK on antral contractile activity are not clearly defined. In contrast to dogs, human gastric emptying is not appreciably delayed by CCK (93,98). Other hormones such as gastrointestinal inhibitory peptide and vasoactive intestinal peptide are released postprandially and cause gastric body relaxation (95). While nerves and hormones have been studied for their separate effects on gastric emptying, probably both are involved in the control of gastric emptying.

Intestinal control: receptors - Much evidence exists to support an intestinal but not a gastric location for the control of liquid meal emptying. Meals containing fat or hyperosmotic (> 285 mOsm/L) concentrations of solutes normally empty slowly, relative to water. However, if the gastric effluent is allowed to drain through an orad duodenal fistula, these meals empty rapidly (76,84,105,106). Thus the rate of gastric

emptying of liquids is dependent upon meal interaction with the intestine. The stomach alone does not respond to variations in meal osmolarity or fat content.

Receptors for osmolytes and fats are located in the small intestine. The term receptor refers to an, as yet, poorly characterized control element; receptor in the classic pharmacological sense is not implied. Diversion of fat from the intestine (via orad duodenal fistula) results in a rapid emptying. Emptying is returned to its usually slow rate by reinjecting fat into the duodenum directly (80,81). Experiments with osmolytes are yet more informative regarding the location of the intestinal receptor. The controlled gastric emptying of meals containing disaccharides and dipeptides depends on their cleavage to osmotically activity monomers. Equiosmolar solutions of maltose (dimer) and glucose (monomer) empty at the same rate (107); the same applies for meals of glycine (monomer) and diglycine (dimer) (108). The cleaving enzymes for disaccharides and peptides are located in the brush border and cytosol of the intestinal enterocyte, respectively. The importance of enterocyte-associated enzymes to osmoreception is highlighted by Mallinson's (109) report of uncharacteristically rapid emptying of

meals containing galactose (a dimer) in patients with lactase deficiencies. Thus intestinal receptors are located deep to, or near the absorptive epithelia.

In both man and dogs, only the orad small intestine responds to meal components (81,87,88,98). Regional sensitivities to certain meal components have been identified. In man, perfusion of the duodenum with hyperosmotic liquids slows gastric emptying; similar perfusions of the jejunum have little effect (98). In contrast, dogs exhibit sensitivity to osmolytes and fats throughout the duodenum and orad jejunum (87,88). In addition, the orad 5 cm of the canine duodenum appears uniquely sensitive to acid but not fat or hyperosmotic solutions (105). Receptor localization throughout the orad small intestine makes good sense functionally. The intestine modifies gastric emptying to regulate the amount of chyme emptied from the stomach. This presumably maximizes intestine absorptive efficiency.

Intestinal control: receptor model - Interaction of meal components with the intestine dictates the rate of gastric emptying. Specifically, meal fats, proteins and carbohydrates have been postulated to elicit the

gastric emptying. Specifically, meal fats, proteins and carbohydrates have been postulated to elicit the EGR by stimulating an intestinal receptor. Of prime importance are the observations that hyperosmotic liquids empty slowly from the stomach, relative to water; and that meal solutes that freely penetrate lipid bilayers have relatively little effect on emptying rate (110,111). These results suggest that a selectively permeable membrane is involved with intestinal "reception". The receptor is currently envisioned as the lateral intercellular space (LIS) of the duodenal and jejunal villus epithelium (112).

The LIS of the orad intestinal villus epithelium are the spaces that separate the lateral borders of the epithelial cells. The luminal aspect of the space is closed by tight junctions; the serosal aspect is bordered by the basement membrane. In addition to the transmembrane route, the LIS provides a route by which water may be both absorbed and secreted. Early observations by Hunt (110,111) concerned the effect of meal osmolarity on the intestinal receptor, which he modeled as an erythrocyte-like structure. Water meals emptied rapidly and were taken as the control. Hyperosmotic meals emptied more slowly than water and

hamster jejunal mucosa with iso- and hyperosmotic solutions resulted in the swelling and collapse of the LIS, respectively. The erythrocyte analogy may have been correct.

If reductions in the LIS dimensions trigger the EGR, this stimulus must be transduced to constitute the afferent portion of the reflex. Secretin and CCK, and postganglionic sympathetic nerves have been cited as possible participants in the reflex. Since both hormones and nerves have been identified in the intestinal mucosa, transductions appear likely. No direct work has been done to relate changes in LIS dimension with hormone or neural changes.

Intestinal control: Effects of osmolytes - Using the semipermeable lipid bilayer as a model, Hunt (110,111) examined the slowing effect of nonpenetrating, freely penetrating and slowly penetrating solutes on the gastric emptying of a water meal. Equiosmolar meals containing nonpenetrating species such as sulfates, KCl, and sugars delayed gastric emptying equally (114-116). In contrast, the addition of freely penetrating NH_4Cl, had no effect on emptying. Slowly penetrating solutes such as glycerol and ethanol only modestly

slowed emptying (110,111). The osmoreceptor model is attractive for its simplicity. That equiosmolar solutions of unrelated, nonpenetrating species (electrolytes and sugars) are equally effective in delaying gastric emptying supports a general osmoreceptor model.

Intestinal control: Effects of fatty acids - Dietary fats are hydrolyzed to their constituent fatty acids by pancreatic lipases. The addition of fatty acids to water meals slows gastric emptying (117,118). Fatty acids to delay gastric emptying by eliciting the EGR, i.e., antral motor activity decreases and duodenal activity increases. The usual motor gradient is reversed (86).

Hunt has proposed that fatty acids, like osmotically active particles, initiate the EGR by shrinking the LIS (112). However, instead of setting up an osmotic gradient, fatty acids may affect the LIS by binding calcium. Calcium is critical to the repair and maintenance of gastric (and presumably intestinal) epithelial surfaces and tight junctions (119). Removal of tight junction calcium by fatty acids is postulated to open the junction and cause water loss from the LIS

(112). If calcium is the key, calcium binding agents that are unrelated to fatty acids should bind calcium and slow gastric emptying. As predicted, sodium dioctylsulfosuccinate (detergent), potassium myristate (C-14 fatty acid), and sodium ethylenediamine tetra acetic acid (calcium complexing agent) each have been found to profoundly slow gastric emptying (120,121). However, the effects of calcium-binding agents on the LIS dimensions have not been established. Further, correlation of calcium binding potency with the ability to delay gastric emptying has not been reported for most fatty acids.

Intestinal control: effects of tryptophan - Equiosmolar meals of amino acids (essential and nonessential) and dipeptides slow gastric emptying equally (108,115,122). However, at concentrations less than 100 mM, meal osmolarity is not affected by the addition of amino acids and gastric emptying is not slowed by their presence (122). The exception, tryptophan, retains a potent inhibitory effect on gastric emptying even at low concentrations. This inhibition is stereoselective for the L-isomer. Further, tryptophan's effect depends upon transmembrane

transport since methionine, which competes with tryptophan for a transport protein, inhibits the slowing effect of tryptophan on gastric emptying (122).

The effects of tryptophan on LIS dimensions have not been studied. However, both tryptophan and fats are potent stimulators of CCK release, and exogenous CCK slows gastric emptying (at least in dogs). Tryptophan's effect may be independent of the LIS.

Intestinal control: effects of acid - Exposure of the duodenum and jejunum to gastric acid or exogenous HCl elicits the EGR (82,87). Cooke (105,106) demonstrated that the gastric emptying of water was markedly delayed after acidification of the meal, or by concomitant perfusion of the intestine with acidic solutions. As the hydrogen ion concentration of the meal increases, the gastric emptying rate decreases to deliver a constant, manageable number of mEq of acid to the duodenum (106,123). The mechanism of acid stimulation of the duodenum is not clear. Hunt and Knox (124) demonstrated that both strong ($pk < 2$) and weak ($pK > 3$) acids slow gastric emptying. The molecular weight of the weak acids influences their effect; as the molecular weight increases, the effectiveness in

slowing gastric emptying (mN basis) decreases (125). In contrast, strong acids are equi-effective irrespective of their molecular weight (110,123-125). Whether acid interacts with the LIS or another type of receptor is not known. Osmoreceptors are not involved since strong acids cause a more profound slowing of emptying per osmol than osmolytes (110). Permeation of the LIS by acid does not appear to be involved since lipophilic hexanoic acid is substantially less effective in slowing emptying than the less lipophilic acetic acid (125). The possibility that both weak and strong acids react with the chloride of mucosal and pancreatic origin to yield only HCl at the receptor is currently under investigation.

Intestinal control: effect of meal caloric density - The addition of glucose, proteins and fats to meals has a delaying effect on the rate of gastric emptying. Each food component is postulated to interact somehow with a duodenal receptor - the LIS. Despite the abilities of food components to delay emptying, fats are more potent (mM basis) than carbohydrates or proteins (126). Since fats exhibit greater caloric density (9 KCal/gm) than protein or carbohydrate (4

KCal/gm), it has been suggested that the controls of gastric emptying can be unified and explained on the basis of test meal caloric density alone (126-128).

As test meal caloric density increases, the rate of gastric emptying decreases (126,127). Thus, glucose solutions of increasing concentration empty at progressively slower rates on a ml per minute basis (127). However, if this emptying is plotted as Kcal emptied vs time, the emptying curves for different glucose meals assume identical slopes, i.e., rates of emptying. A constant delivery of calories to the duodenum means that larger meals will take longer to empty completely. This contrasts with the gastric emptying of noncaloric, isotonic saline which empties faster (ml/min) as meal volume increases (99). Constant caloric delivery probably also occurs with fats. Although little work has been done, isocaloric meals containing fat, glucose, and protein have been shown to empty at identical rates, based on Kcal emptied per time (127). Despite the attractiveness of a unified mechanism for the control of gastric emptying, it should be noted that osmoreception may occur independently of calorie detection. Hyperosmotic saline and glucose solutions each empty from the

stomach more slowly than their respective isosmotic counterparts (110,112).

Several themes described so far resurface in the accompanying research reports.

1) The stomach and small intestine each exhibit periodic motor activity in the fasted state. The period of motor quiescence (phase 1) may be employed for determination of the motor responses to test meals.

2) Gastric emptying is the end result of a gastric-to-duodenal intraluminal pressure gradient. This gradient is the result of gastric and duodenal motor activity. Meal components stimulate the intestine to modify gastroduodenal motor activity, and gastric emptying.

3) In the fasted state, an interval of intense contractile activity appears first in the stomach and then migrates to the terminal small intestine. This activity is presently thought to sweep indigestible meal residues from the stomach.

3. HYDROPHILIC POLYMERS

Overview:

Hydrophilic polymers broadly describes a select group of compounds that have traditionally been classified as bulk-forming laxatives. In particular, dietary fibers such as psyllium and the synthetic polymer polycarbophil belong to this class. Recently, dietary fiber has received attention as an adjunct in the dietary management of postprandial glycemia in diabetics (review see 129). Certain evidence suggests that dietary fibers may act to attenuate postprandial glycemia peaks by delaying the gastric emptying of meal carbohydrate. In addition to psyllium, several nonlaxative fibers such as pectin and guar gum have also demonstrated this effect. This new therapeutic application of fiber shifts interest from their laxative properties to their effects on gastric emptying.

Hydrophilic polymers: chemistry - The structural formulae for psyllium, pectin, guar gum and polycarbophil are detailed in tables 1 and 2. Complete chemical definition for plant-derived polymers is

FIGURE 2.

Idealized rheograms for Newtonian, pseudoplastic, plastic and dilatant systems.

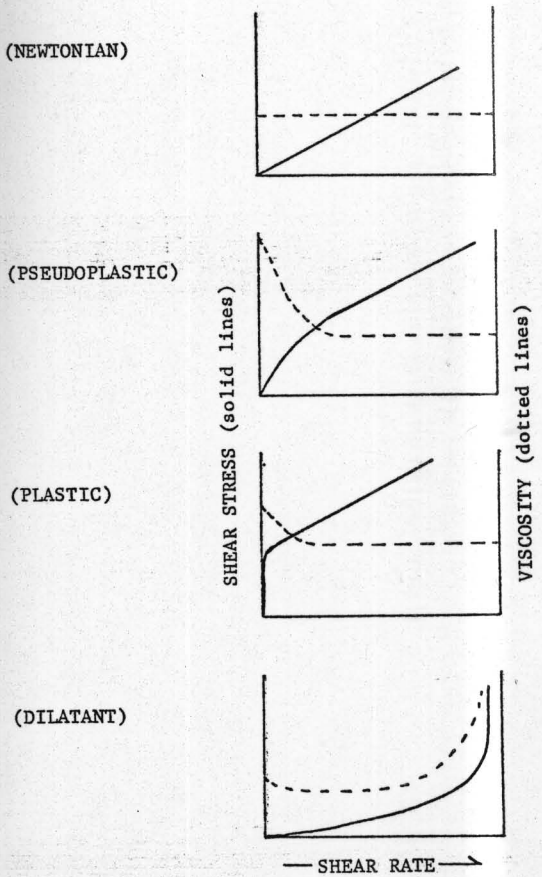
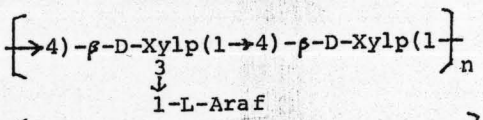
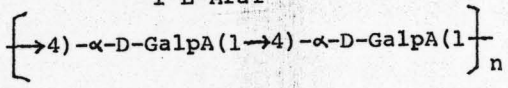
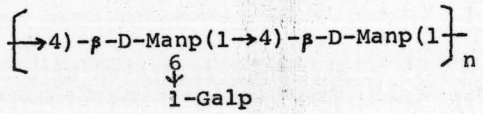

(NEWTONIAN)
(PSEUDOPLASTIC)
(PLASTIC)
(DILATANT)
SHEAR STRESS (solid lines)
VISCOSITY (dotted lines)
SHEAR RATE

Table 1.

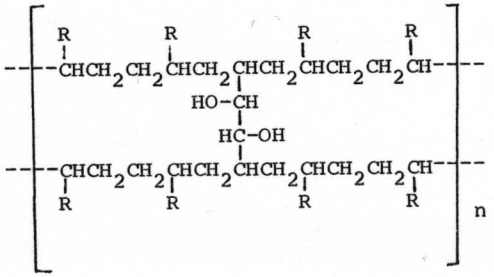
Structural formulae for hydrophilic polymers.

Polymer	General Formula
psyllium	
pectin	
guar gum	

Xylp: xylopyranose
Araf: arabinofuranose
GalpA: galactopyranose, acid form
Manp: mannopyranose
Galp: galactopyranose

Table 2.

Structural Formula for Polycarbophil.



R= CO_2^- Na^+

lacking. However, for the agents under study, certain information is available.

Historically, guar has been described as a gum while psyllium has been described as a mucilage. For the purposes of this review (and for probably all purposes, 130) the terms are synonymous and gum will be used. Gums refer to any of the variety of water-soluble, complex polysaccharides which act to prevent the dessication of plants or their seeds. Water-insoluble exudates (resins), waxes and proteins may also serve in this protective capacity (130).

Psyllium is comprised of the milled husks and seeds of Plantago ovatus, P. indicum, and P. psyllium (131). The gel-forming polysaccharide is composed of a linear backbone of xylose units, with side units of arabinose, xylose, glucuronic acid and glucose (table 1, review see 132). Patterns of side unit substitution are not always apparent. The purified gum is water Hydration of the polysaccharide yields a gel of concentration-dependent viscosity (vide infra, 130). Commercially available psyllium (Metamucil,(R) G. D. Searle & Co.) contains seed husks and an equal weight of dextrose as a dispersing agent.

Guar gum is obtained from the endosperm portion of

the seeds of Cyamopsis Tetragonalbus (130). Guar is apparently chemically simpler than psyllium. The guar polymer backbone includes a chain of B-(1T4)-linked mannonse units with a D-galactose substituted at every other mannose (130,132, table 1). The polymer strands tend to have a molecular weight of about 250000. Guar gum is water soluble; as the concentration increases guar yields an opalescent suspension.

Pectin is a carbohydrate polymer associated mainly with the intercellular spaces and cell walls of seeds. Pectin is found in the rinds and pulp of citrus and non citrus fruits, respectively (132,133). Pectin content varies widely with its source (apple pulp: 17%; citrus peel: 33%). In addition, the chemical heterogeneity of pectin is plant species-dependent. Sunflower pectin is probably the most homogeneous. It consists of polymer strands of galacturonic acid (table 1). More commonly, pectins have 1-2% rhamnose residues incorporated into the galaturonate backbone. Side groups are of varying lengths. Arabinose, galactose, rhamnose and xylose residues are frequently present (132). Usually, a percentage of the free carboxyl groups are methoxylated. Pectin normally presents as a high (7-14%) or low (< 7%) methoxy form. High methoxy

high (7-14%) or low (< 7%) methoxy form. High methoxy pectin gels when it is combined with more than an equal weight of sugar; the pH must be adjusted to about 3 or 4. Low methoxy pectin forms a gel in the absence of sugar, but its gelling is critically dependent on the presence of a cation, usually calcium (133). Low methoxy pectin gels retain viscosity over pH range 2 to 7. Pectin is water soluble.

Polycarbophil is not a dietary fiber. It represents a class of cross-linked polymeric organic acids patented for their hydrophilic properties (134). Polycarbophil consists of cross-linked polyacrylic acid strands (table 2). The pH and ionic strength of the hydrating medium affect hydration (135). At constant pH, the progressive addition of NaCl to the water (up to 0.9%) reduces the maximum degree of water absorption by a factor of 4. In a medium of constant ionic strength, polycarbophil will exhibit a tremendous increase in water absorption when the pH is raised from 4 to 7. One gram of polycarbophil will absorb 75 ml of water at pH 4, and 500 ml at pH 7 (AG Robins, personal communication). Since gastric and intestinal secretions tend to be isotonic, regional pH differences in the gut likely

form the basis for polycarbophil's bulking effect in the small and large intestine (pH ca 5-7), relative to the stomach (pH ca 2).

Flow behavior of hydrated polymers - Guar, psyllium and pectin exhibit varying degrees of water solubility at low concentrations. Despite solubility differences, each of these compounds is hydrophilic and absorbs water. Specifically, each agent incorporates water into its polymer matrix and holds it to form a gel. Gels are defined as colloidal dispersions of a solid phase within a liquid phase (136, 137). Although particle size has been suggested as a criterion for classification as a colloid (1-500 mu), flow properties may also help identify gels (vide infra). Gels differ from other colloids in that they can exhibit a reversible tendency to flow. Upon standing, gels present as a semi-rigid mass. After agitation they flow freely. Subsequently, upon standing they revert to the rigid form. The dispersed solid phase may exhibit variable solubility in the dispersion medium. Note that the preparations under investigation demonstrate gel properties, but are macromolecular or coarse dispersions. This is a result of the size of

the polymer molecules involved (molecular weight commonly 250000). Unhydrated plant residues (husks) may also be present as in the case of psyllium.

The gels of psyllium, pectin and guar present as semisolids after standing. Upon agitation, each gel exhibits less resistance to flow. Once agitation ceases, the semi-rigid form reappears. This gel-sol-gel transformation highlights the main rheological features pertinent to the present investigations, namely, viscosity and nonNewtonian flow.

Viscosity is an expression of the resistance of a fluid to flow (136,137). Viscosity is conceptualized as the ratio:

$$\frac{F}{A} = \eta \frac{dv}{dr}$$

where F/A is the shear stress or force per unit area required to initiate flow; η is the coefficient of viscosity; and dv/dr is the shear rate, or velocity gradient between 2 planes of liquid separated from each other by an infintesimal distance. The equation may be rearranged as:

$$\frac{(F)(dr)}{(A)(dv)} = \eta$$

and since:

$$\frac{F}{A} = \frac{\text{dynes}}{\text{cm}^2}, \text{ and } \frac{dv}{dr} = \frac{\text{cm/sec}}{\text{cm}}$$

by substitution into the original equation viscosity takes the units of

$$\frac{(\text{dynes})(\text{cm})}{(\text{cm}^2)(\text{cm/sec})} = \eta = \frac{\text{dynes}}{\text{cm}^2\ \text{sec}}.$$

The unit of viscosity is the poise. By definition, 1 poise is the force required to produce a velocity of 1 cm/sec between 2 parallel planes of fluid, each 1 cm^2 in area, and separated by a distance of 1 cm. Most viscosities are reported as centipoise (cp). For many purposes, water has a viscosity of 1 cp.

Flow systems are described as Newtonian or nonNewtonian. Newtonian systems are typified by water. As the shear stress applied to water increases, the rate at which it flows increases (fig. 3-a). As predicted from the equation, viscosity then is constant irrespective of the shear stress applied. Newtonian systems may exhibit any viscosity; the slope, i.e., shear stress-to-shear rate ratio can vary. However,

proceeds along a straight line. In contrast, nonNewtonian systems deviate from this simple relation. The terms pseudoplastic, plastic and dilatant describe various nonNewtonian relations, and each term refers to a general case where the shear stress-to-shear rate relation deviates from linearity (fig. 3).

When studying the effects of shear stress on the shear rate of a fluid, it is necessary to keep either stress or rate at a controlled value. Customarily, the rate of shear is controlled. The fluid to be tested is loaded into a reservoir and subject to the frictional forces caused by a rotating spindle (further information, see chapters 2,4). Rotation of the spindle forces the fluid to flow at a controlled rate. The shear stress which is overcome to produce flow is the measured variable. As an aid to identifying the viscosity changes that accompany flow rate changes as measured <u>in vitro</u>, viscosity is also plotted against shear rate (fig. 3).

Pseudoplastic systems are commonly represented by colloidal dispersions of soluble and insoluble polymers. Increases in shear stress produce immediate increases in shear rate (fig. 3). However, the

increase in shear rate is not marked until sufficient shear stress is achieved. After sufficient stress is applied, pseudoplastic systems exhibit Newtonian-like behavior. The initial resistance to flow is overcome in at least 3 ways. First, hydrated polymers normally exist in a semispherical arrangement. Upon shear the hydrated polymers are elongated and oriented in the direction of flow. Second, this reorientation prevents much interparticle water from being dragged along with the polymers. Finally, the elongated chains further tend to disentangle under stress.

Plastic flow is indicated when a substantial increase in shear stress is required to initiate flow (fig. 3). Dispersions of particles which are flocculated, i.e., electrically attracted to each other, commonly exhibit plastic flow. The stress required to initiate flow is termed a yield value. This value represents the stress required to break interparticle electrostatic bonds. Once flow is achieved, further increases in shear stress result in increased shear rate; the system becomes Newtonian.

Dilatant flow occurs when gradually increasing amounts of shear stress cause gradually decreasing rates of shear (fig. 3). This form of flow can occur

with high concentrations of small deflocculated solids (deflocculated particles electrically repulse each other; they contrast with the flocculated particles normally constituting plastic systems). At low rates of shear, interparticle water is thought to adequately wet each particle; particles then pass each other with relative ease. As shear stress increases, the overall volume of the gel mass increases presumably due to the introduction of air into the intermolecular spaces. The water available becomes insufficient to adequately wet the particles. Interparticle friction increases with increasing shear stress and gel viscosity is seen to increase markedly (Fig. 3).

Application of shear stress to particle dispersions results in the deformation of the spatial arrangement of the dispersed particles. Brownian movement tends to return the particles to their pre-agitation or gel arrangement. This balance is constantly acting. The gel structure is either restored immediately or after a period of time. Time-dependent restoration is termed thixotropy (for comprehensive reviews of rheology see 136, 137).

Certain flow characteristics of gel-forming fibers such as guar gum, psyllium and pectin have been

such as guar gum, psyllium and pectin have been reviewed (131). In general, gel viscosity is stable over a wide range of pH values (psyllium and guar: pH 2-10, ref. 130; pectin: pH 2-7, ref. 133). Acid-stable viscosity is of importance to the gastric emptying properties of gels (vide infra, chapter 2).

Polycarbophil is insoluble in water. Like psyllium, pectin and guar, polycarbophil is hydrophilic. However, polycarbophil is not a gel in the same sense that the other agents are. In its dessicated state, polycarbophil presents as granules whose size is determined strictly by milling. Upon hydration, each granule yields a larger, transparent particle. A meal of polycarbophil particles in water presents as a collection of these particles plus any unincorporated water. The gel particles are discontinuous with respect to each other and do not display a recognizable flow system. Theoretically, hydrated particles of small enough dimension might behave as a dilatant system mainly because the particles are easily separated from unassociated water, and because their discontinuous hydrated form would favor interparticle friction (Dr. H. S. Chen, personal communication)*. Despite not exhibiting gel-sol-gel

transformations, polycarbophil and other similar hydrophilic polymers are commonly referred to as gel-forming. This is based strictly on the hydrophilia and gel-like appearance of the polymer after hydration (139). In the present studies, polycarbophil is referred to as a discontinuous gel, or as gel particles.

Not all dietary fibers are gel-forming. Plant fractions that are devoid of or are low in gum content, e.g., bran are relatively non-hydrophilic (138). Upon mixture with water, bran remains in a separate phase. As such, fibers such as bran and alpha cellulose resemble polycarbophil. Bran, alpha cellulose and polycarbophil do not exhibit a recognizable flow system; they behave as solids.

Effects of hydrophilic polymers on gastric emptying

While the effects of fiber on the gastric emptying of test meals is of interest, the emptying characteristics of the fibers themselves are also important (vide infra, chapters 1 and 3). Specifically, a knowledge of how homogeneous gels and particulate solids alone empty would help predict how they would affect the gastric emptying of conventional meal solids and liquids. A prerequisite for assessing

the gastric emptying of both particulate solids and homogeneous gel-forming fibers is a meal-specific marker. Radioactive markers for bran and alpha cellulose have only recently been developed (102, 158), and no information is available concerning their individual emptying characteristics. Markers for, and the gastric emptying of gel-forming fibers and particulate solids (polycarbophil gel particles) are presented in chapters 1 and 2 (vide infra). The following 2 subsections concern the limited information available on the effects of gel-forming and nongel-forming fibers on the gastric emptying of test meals.

The addition of the gel-forming dietary fibers guar gum, pectin and psyllium to carbohydrate-containing meals attenuates postprandial glycemia (140-151). Such an effect is of considerable usefulness in the dietary management of diabetic patients (review see 129). Because meal carbohydrate must first be delivered to the small intestine and then absorbed, attention has been focused on the ability of fiber to delay both gastric emptying (vide infra), and intestinal absorption (152-155). Only the effects of fiber on gastric emptying are discussed here. As pointed out earlier, the fibers pectin, psyllium and

attention has been focused on the ability of fiber to delay both gastric emptying (vide infra), and intestinal absorption (152-155). Only the effects of fiber on gastric emptying are discussed here. As pointed out earlier, the fibers pectin, psyllium and guar hydrate to form viscous, homogeneous gels. In contrast, the fibers wheat bran or alpha cellulose do not form gels; they retain their particulate form in water. Despite physical differences, particulate solids and homogeneous gel systems both reduce postprandial glycemia (142, 152, 156). Both fiber types may affect the gastric emptying of test meals.

Direct evidence for the ability of fibers to delay gastric emptying of meal solids and liquids is only slowly accumulating. The paucity of data extends mainly from the lack of adequate markers for digestible meal components. Most work concerning the gastric emptying of digestible solids has been performed since Meyer (197) reported the radiolabeling of liver. Since that time, 1976, markers for starch and oil phases of meals have been advanced. However, little information concerning the effects of fiber on labeled meal components has been generated (146).

Indirect and direct evidence for fiber-related delays

of gastric emptying - Gel-forming fiber can delay the gastric emptying of liquid (148-151) and solid (146) test meals. Indirect evidence supports this effect. Past studies have demonstrated that the addition of guar (140,142,147), pectin (140,143,150), guar plus pectin (148), and psyllium (144) to liquid carbohydrate meals each was able to reduce postprandial serum glucose elevations. In some cases this was accompanied by a partial or complete delay in postprandial glycemia (140,147,148,150). In addition, postprandial elevations of breath hydrogen, taken as an index of oral-to-cecal transit time were markedly delayed by pectin (143), psyllium (149), and guar (142). Results from these studies suggest a delay in the gastric emptying of meal carbohydrate. However, both blood glucose and breath hydrogen assays incorporate confounding variables into the estimate of gastric emptying. Gels inhibit the intestinal absorption of glucose (153,154); thus estimates of emptying delay will be inflated. Oral-cecal transit measures the arrival time of the head of a carbohydrate meal to the cecum/colon (159); estimates of gastric emptying again are inflated due to the sometimes considerable small intestinal transit time. In addition, no information

is given concerning the completeness of meal emptying with either assay. Nonetheless, a major change in either parameter is consistent with a delay of gastric emptying.

Direct measurements of the effect of fiber on gastric emptying have been described in just 5 reports. Pectin and psyllium have each been shown to delay the gastric emptying of liquid test meals. In patients with pathologically rapid gastric emptying, "dumping", the addition of pectin caused a doubling of the half-emptying time (E 1/2) from 12 to 28 min (150). In surgically intact patients, a psyllium meal emptied more slowly (E 1/2 ca 25 min) than a water control meal (E 1/2 ca 10 min) (149). The addition of guar gum to a gruel meal also doubled the meal E 1/2 (147). In other studies, combinations of guar plus bran (146) and guar plus pectin (148) both increased meal emptying times.

Although the addition of gel-forming fiber to meals delays emptying, data which help explain how fiber exerts this effect are lacking. Meal fiber type and content are both probably important to the effect. The effects of increasing meal fiber concentration on gastric emptying (or postprandial

glycemia) are unknown. Various concentrations of guar can delay emptying (147,150,157), and increased meal viscosity probably is responsible (142). Intuitively, an increase in meal gel-forming fiber should yield a thicker meal which will empty more slowly. Gel-forming fibers do exhibit concentration-dependent viscosities (130). A viscosity-related delay in the emptying rate of potato meals has been reported (160). However, systematic assessment of the effects of increasing fiber content on the gastric emptying of a standard meal, e.g., saline or nutritive liquid, have not been performed.

The ability of fiber to slow gastric emptying of both liquid and solid phases will be affected by the phase with which the fiber was originally mixed (solid, liquid or both). Liquids empty rapidly and solids are held back until liquified. Gel-forming fibers may affect this process. One study to date documents the ability of guar gum to slow the gastric emptying of both liquid and solid phases of a meal (146). However, close inspection of the data reveals that most of the liquid continues to empty in the pretreatment manner; only the solid was slowed importantly. The thoroughness of

mixing in the stomach, and the water content of the meal (affecting gel viscosity) will determine how each meal phase is affected.

Nongel-forming fibers may also affect gastric emptying of meal carbohydrate since the addition of bran to liquid test meals reduces postprandial glycemia (142). However, the effects of bran or alpha cellulose on the gastric emptying of liquids have not been directly tested. Both bran and alpha cellulose may be considered to be indigestible solids. Whether small particles of bran or alpha cellulose empty with or after meal liquids is unknown. Based on the rapid gastric emptying of meal liquids, relative to digestible and indigestible solids (vide supra), bran and alpha cellulose should empty more slowly than liquids. As with gel-forming fibers, particulate fiber type and meal concentration will likely affect changes in the emptying of meal liquids.

The effect of nongel-forming fibers on the gastric emptying of meal solids has not been studied. However, the labelling of digestible solids such as liver has been reported (161). Thus, a tool for measurement of fiber-related changes in gastric emptying of solids is available.

A model for indigestible food residues - Conventional meals contain liquids, digestible solids and indigestible solids. These components empty from the stomach at different rates, and with different patterns (see gastric antrum pp. 22). While the gastric emptying of liquids and digestible solids has been extensively studied, the gastric emptying of indigestible solids has been essentially ignored. This is probably a reflection of the only recent interest in the effects of indigestible ingesta, i.e., dietary fibers, on upper gut function.

The gastric emptying of indigestible food particles is currently modeled using large (7 mm diameter) spheres (vide supra). Whether spheres are administered alone or with a meal, they always empty after the liquid and solid fractions. Emptying is always pursuant to the reappearance of interdigestive phase 3 contractile activity (57).

In contrast to spheres, the gastric emptying of other indigestible materials has not been directly investigated. Two studies strongly suggest that the phase 3-dependent gastric emptying of spheres does not adequately model the gastric emptying of indigestible

meal components such as dietary fibers. The addition of milligram amounts of alpha cellulose (102) or 50 gm of labelled bran (158) to digestible solid meals reveals that the fiber-meal mixture empties steadily and slowly from the stomach. There is no evidence that the fiber is segregated in the stomach for preferential emptying after liquids and solids. Further, the emptying pattern did not suggest a dependence on the reappearance of interdigestive phase 3 activity for its exit. These data and those obtained with spheres suggest that particle size may determine the rate and pattern of gastric emptying of indigestible ingesta. Since the gastric emptying of spheres and fibers is so different in the cases cited, the adequacy of spheres as a model for (usually smaller) indigestible particles is questionable.

Effects of hydrophilic polymers on intestinal motility - Certain hydrophilic polymers, and in particular certain dietary fibers, act as bulk-forming laxatives. Treatment with bulk-forming laxatives is associated with major changes in colonic motor patterns. The effects of bulk-forming laxatives on small intestinal motor activity are not known. The

possibility that bulk-formers elicit propulsive small intestinal motor patterns could bear on their laxative properties. In addition, though not considered here, motor changes favoring hastened transit would also relate to the ability of certain dietary fibers to impair intestinal absorption and digestion (review see 155).

In the following 4 subsections the very limited current knowledge of how hydrophilic polymers affect large and small intestinal motility is detailed. An investigation of the effects of hydrophilic polymers on jejunal motility is presented in chapter 4.

Relationship of motility to transit: effects of laxatives - Transit through the gut is profoundly influenced by contractile activity. For example, gastric phase 3 contractions control the gastric emptying of indigestible spheres; and jejunal phase 3 activity pushes a marker aborally while the marker fails to migrate during the period of motor quiescence (162). Drugs help highlight the relation between motility and transit. Morphine elicits nonpropulsive contractions of the small intestine in dogs (163). In rats, morphine depresses all contractile activity

(164). Both nonpropulsive contractions and motor quiescence are accompanied by a slowed transit. Laxatives also alter motility-transit relations.

Laxatives are chemically diverse substances used either to increase stool frequency or alter its texture (165). Laxatives may be broadly classified as secretogogue, bulk-forming, osmotic or emollient type. Most laxatives are either of the secretogogue or bulk-forming variety.

Until recently, all laxatives were thought to exert their effects in the colon (166). Over the past decade, the secretogogues were discovered to act in the small intestine (review see 167). In brief, secretogogue laxatives such as castor oil destroy small intestinal absorptive epithelium; secretion outbalances absorption, and small intestinal propulsive motor patterns appear (167-169). Frequent, watery stools are associated with these laxative-induced motor patterns. The ability of the colon to absorb water is overwhelmed by the delivery of intestinal secretions, resulting in laxation.

Hydrophilic polymers as laxatives - All bulk-forming laxatives are hydrophilic polymers, and many hydrophilic polymers are dietary fibers. In contrast to secretogogue laxatives, bulk-formers have not been shown to elicit small intestinal secretion or watery diarrhea. Instead, bulk laxatives increase stool volume. This effect has been positively associated both with a reduction of transit time through the gut, and aborally-propagated colonic motor patterns (vide infra).

Laxation, or increased frequency of stool passage, is equated with a reduction of transit time through the gut (usually mouth-to-anus). Total transit time may be assessed radiographically or by monitoring the recovery of an unabsorbable marker. in most cases, indigestible radiopaque pellets are incorporated into meals. The recovery of pellets from the stools with time reveals the speed with which a column of colonic material passes through the colon (170-172, review see 173). Transit time is primarily a colonic event since the gastric emptying and intestinal transit of a conventional meal takes 4-6 hours while the typical recovery time of a marker load averages 1-3 days (174-176).

Bulk-forming laxatives cause increases in stool weight and decreases in transit time. The positive association between increased rate of transit and increased stool weight has been most strongly established for bran (177,178, review see 152). The agents presently under study - psyllium, polycarbophil and guar - have not been extensively investigated. However, psyllium and polycarbophil each increase stool weight (175,179) and frequency (179,180,181). In contrast, guar has negligible effects on stool weight and transit time (174). Like guar, pectin neither increases stool weight appreciably, nor does it reduce transit time (176,182-185). As such, pectin and guar have little usefulness as bulk-forming laxatives.

Fiber digestibility probably affects stool volume. As fiber digestibility increases, stool volumes seem to decrease. Pectin is totally degraded by colonic microflora and has no demonstrable effect on stool size (176,182-185). In contrast, bran and alpha cellulose are less digestible (176,186) and are associated with greater stool weights (174,175,177, 187). Increases in stool weight are likely the combined result of an increase in colonic bacterial mass, residual indigested fiber, and fecal water bound

to the fiber residues (186).

Bulk-forming laxatives elicit gut motor changes both when given alone or when mixed with a meal. Only a few studies have focused on motility effects. Specifically, one study deals with small intestinal responses and 5 studies deal with colonic motor effects. The effects of fiber on colonic motility are described first, followed by small intestinal effects. Both groups of results emphasize the deficiencies present in the current knowledge of the effects of hydrophilic polymers on small intestinal motor function.

Effects of hydrophilic polymers on colon motility - Certain colonic motility patterns are common to man (188-190), dogs (191,192) and pigs (193). Two basic electric rhythms (BER) have been described (dog: 5 and 11 cpm; man: 3 and 10 cpm). Although spike potentials are superimposed upon both BER, their appearances are not rigidly phase-locked. High frequency spike potentials (short spike bursts, SSB) have no significant contractile correlate (191). In contrast, spike potentials associated with the slower BER frequency herald phasic contractions of variable

duration (6-25 sec) and amplitude (long spike bursts, LSB, 188,189). LSBs appear in groups, with one group lasting from 5-15 min. Groups of LSBs propagate, usually aborally and are called migrating spike bursts (MSB) (191). MSB activity predominates during normal or fiber-enhanced transit while SSB activity predominates in patients and animals with low fiber diets or constipation (significantly delayed transit time) (188,189,192,193).

Bulk laxation affects colonic motility. Burrows and Merritt (191) demonstrated that progressive increases in dietary alpha cellulose resulted in briefer (i.e., reduced from 11 to 8 min duration), but not more frequent or more rapidly propagated episodes of MSB activity in dogs. Stool weights increased (4-fold) and transit times decreased (37 to 29 h) as fiber intake increased. The shortened MSB intervals at higher fiber levels may have reflected a more effective propulsive contractile activity. Since the ability of the colon circular muscle to develop tension is enhanced after stretching (equivalent to colon distention?) an increase of stool volume probably helped to effect this altered contractile response (194,195). Whether cellulose-shortened MSB intervals

represent more efficient propulsion, as might be expected with a hastened transit, has not been determined.

In other studies the effect of fiber on the preponderance of LSB activity, relative to SSB activity was examined; patterns of activity were not considered. LSB activity (like MSB activity) is associated with bulk laxation. In dogs (192) and pigs (193), the absolute number of proximal colonic LSBs is dramatically increased with increases in fiber intake. In pigs, maximum fiber levels are accompanied by reduced transit times and increased stool weights, relative to fiber-free diets (193). In dogs, maximum fiber intake is also accompanied by increases in stool weight and a decrease in intracolonic transit time(192). In both species, as fiber intake decreases, transit times increase and SSB activity becomes predominant. (NB: intracolonic transit is measured from the orad to mid-descending colon. Normal canine colon residence time of a marker is probably 20-30h, 187). A pretreatment control value of 5 hours suggests that the surgical model - dogs with colostomy - demonstrates marked altered baseline colonic transit. Even so, the relation between LSB activity,

transit, and bulk laxation resembles that seen in intact humans and dogs).

Despite a probable association between LSB activity and bulk laxation, much remains unknown. For example in dogs, increased numbers of LSBs after treatment with bran (192) contrasts with the unaltered number of LSBs after cellulose (191), yet both agents reduce transit time (175-178, 186, 191, 192). Several factors will influence investigation of this relation. First, colon motility patterns have not been extensively studied. As colonic motility patterns are more completely characterized, comparative assessment of fiber-related motor effects reported by investigators will be easier. Second, differences in experimental models now make comparisons of results tenuous (e.g., intracolonic transit vs total transit; dogs vs. pigs). Third, in most studies of the colon motor responses to fiber, the effects of fiber type and dose have not been assessed. Fiber type and the quantity ingested (the dose-response relation) affect laxation parameters such as stool weight and transit time. Further, fiber form, (bran of large and small particle sizes) is known to affect stool weight (196,197). Thus fiber type, the quantity ingested, the

physical form of the fiber, and the experimental model used will each influence the character and effect that fiber has on laxation and colon motility.

Effects of hydrophilic polymers on small intestinal motility - Only one study to date deals specifically with the effects of hydrophilic polymers on small intestinal motor function. Bueno et al. (198) demonstrated that incorporation of 30 gm cellulose, bran or guar gum into a canned food meal markedly altered canine postprandial jejunal motor responses. Each agent prolonged the duration of the postprandial duodenojejunal motor pattern probably because gastric emptying was slowed. Indexed motor responses remained modest with respect to the amplitude and frequency of contractions. Of interest were fiber-induced patterns of motor activity and the possibility that small intestinal transit might therefore be altered by fiber. However the effects of fiber dose on small intestinal motility were not investigated.

Small intestinal motor patterns can be fiber-specific. Bran and cellulose elicit groups of contractions which migrate aborally (198). In contrast, guar gum elicits almost continuous, low

amplitude contractions. In each case, the fiber-associated pattern differs from the usual random distribution of contractions seen postprandially. Bran, cellulose and guar are each equally effective in eliciting motor activity in the absence of the meal. The reasons for motor pattern differences are not clear. Bueno et al. (198) suggest that the greater ability of guar to absorb water, relative to bran or cellulose is consistent with a difference in motor effects. If so, then pectin and polycarbophil, each having a greater water absorbing capacity than bran (135,138), should elicit effects similar to those of guar. However, polycarbophil elicits a highly organized motor pattern while pectin elicits a disorganized pattern (vide infra chapter 2). Further, the pattern seen with polycarbophil resembles that for bran and cellulose. Bran and cellulose are particulate in appearance, while guar forms a homogeneous gel upon hydration. This raises the possibility that the physical form of the fiber, i.e. whether it presents as particles (bran, cellulose, polycarbophil) or a homogeneous gel (guar gum, pectin) may determine the motor response it elicits.

In addition to polymer form, meal viscosity may

influence small intestinal motor patterns. Fibers such as psyllium and guar form viscous gels upon hydration. Both gel type and concentration will influence viscosity. Whether increases in meal viscosity differentially influences small intestinal contractile activity or patterns is not known. Colonic motor responses to fiber meals are probably not influenced by viscosity since gel-forming fibers such as pectin and psyllium are extensively degraded by colon anaerobes (199,200). Such digestion results in a reduction of gel viscosity (199,200).

STATEMENT OF THE PROBLEM

Limited evidence shows that hydrophilic polymers delay the gastric emptying of liquid and solid test meal components. Precisely why they alter gastric emptying has not been determined. The gastric emptying characteristics of meals of hydrophilic polymers alone would give insight into how polymers affect the gastric emptying of conventional meals. However, measurements of polymer gastric emptying require that the polymers under test be adequately labeled. To date, the labeling of viscous ingesta with markers (e.g.

Several factors will likely influence the gastric emptying of hydrophilic polymers. First, since antroduodenal motor activity gradients intimately influence gastric emptying, they should be characteristically altered by polymer test meals. Second, just as meal solids are selectively emptied according to their particle sizes, particulate and homogeneous gels should empty differently. Finally, the flow properties of gel-forming polymers should influence their emptying rate. Precisely how increases in meal fiber content affect these parameters and perhaps gastric emptying has not been investigated.

In contrast to homogeneous gels, the concept of viscosity is inappropriate for indigestible particulate substances. Particles behave essentially as solids. Currently the gastric emptying of indigestible particulate meal components is modeled using 7 mm diameter spheres. However, indirect evidence suggests that large spheres may be a poor model for the emptying of such meal residues. The gastric emptying patterns of indigestible solids of smaller particle size would help reveal whether large spheres were an adequate model for smaller particles.

Gut motility affects intraluminal transit.

Gut motility affects intraluminal transit. Certain hydrophilic polymers are bulk-forming laxatives with distinct effects on colonic motility and total gastrointestinal transit time. Hydrophilic polymers could have significant effects on small intestinal motility. This possibility has not been examined in detail. Meal polymer type, content and flow properties probably will have distinct effects on the intestinal motor responses to hydrophilic polymers.

The objectives of the following studies were:

1) To develop markers for homogeneous and nonhomogeneous gels of hydrophilic polymers.
2) To characterize the gastric emptying patterns of homogeneous and particulate polymer meals in dogs; also, to assess whether canine postprandial antroduodenal motility and test meal flow properties influence the gastric emptying of polymer meals.
3) To examine the gastric emptying of gel particles as a test of the current belief that the gastric emptying of all indigestible meal residues may be modeled with one substance.
4) To characterize the small intestinal motor

nonhomogeneous hydrophilic polymers.

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CHAPTER 2

Method for the Quantitation of Gastric Emptying Time of Gel Test Meals.

ABSTRACT

Isotopic markers were developed to allow measurement of the gastric emptying times of homogeneous and nonhomogeneous gel meals. Meals containing the dietary fibers psyllium and guar gum presented as homogeneous, viscous gels while meals containing the synthetic polymer polycarbophil presented as discrete gel particle-water mixtures. Fiber meals were labeled differently than polycarbophil meals.

Fiber meals were labeled with ^{51}Cr-CM-Sephadex. The marker was insoluble and was uniformly suspended in meals containing at least 1% guar or 2% psyllium. In contrast, the polycarbophil meal was labeled with water-soluble $Na_2{}^{51}CrO_4$. The isotope bound tenaciously and specifically to the polycarbophil gel particles.

The utility of the markers was demonstrated in dogs fitted with mid-duodenal cannulas. Labeled test meals of guar, psyllium and polycarbophil were each administered orally. Gastric emptying times were based upon: effluent solids (dry weight) collected and the amount of isotope recovered from the duodenal cannula with time. Plots of the cumulative recovery of the meal, as effluent solids or isotope, vs. time showed a gross underestimate of the polycarbophil meal half-emptying time when based upon effluent solids recovered. Psyllium and guar meal half-emptying times were similarly estimated by the use of the isotope marker or effluent solids.

We conclude that ^{51}Cr-Sephadex and soluble Cr-51 may be employed as meal markers for estimation of the gastric emptying times of certain homogeneous and nonhomogeneous gel-type meals, respectively.

INTRODUCTION

The gastric emptying of low viscosity liquids and certain food solids has been extensively studied in both man and the dog (reviews see 1,2). In contrast, the gastric emptying of semisolid meals, such as gels, has received little attention (3,4). Certain dietary fibers, particularly guar gum and psyllium, are gel forming and are currently being advocated as adjuncts in the dietary control of diabetes mellitus (5,6). Few studies have been performed to establish the effects of dietary fiber on the gastric emptying of conventional foods. An understanding of how fiber meals alone empty from the stomach would give insight into how fibers affect the gastric emptying of liquid and solid meal components. To monitor the gastric emptying of these gel-forming fibers would require a suitable fiber meal marker. To date, labels for only alpha-cellulose (7) and bran (8), two nongel-forming fibers, have been reported. To our knowledge no marker has been devised for meals containing psyllium or guar gum.

To be valid, markers for liquid (phenol red, chromium-51) and digestible solid (technetium-99) meal components must be uniformly distributed throughout the meal phase of interest (1,9). Alpha-cellulose is a chemically pure (β-1$\rightarrow$4-linked glucose residues) fiber which is uniformly and therefore adequately labeled by iodination (7). In contrast, guar gum and psyllium are each more chemically heterogenous compounds (10) for which no chemical labeling methods have been reported. However, psyllium, guar and other fibers are partially water soluble and can form viscous gels that will suspend solids (11,12). Just as for

liquid and solid test meals, the labeling of fiber suspensions would require that the marker be uniformly distributed in the suspension irrespective of its association with either the soluble or insoluble fraction of the fiber. Further, the marker must remain with the gel and not be leached from the gel in vivo.

In contrast to psyllium and guar gum, certain polymer molecules can hydrate and gel but not be suspended in the hydrating medium. One such agent, polycarbophil, is a polymer of cross-linked acrylic acids (13). The calcium salt of polycarbophil is employed clinically as both an antidiarrheal agent and a laxative (13). Upon hydration of polycarbophil, a nonhomogeneous system forms where the hydrated gel particles separate from any unassociated water (personal observation). Since liquids empty from the stomach more rapidly than solids (2), the accurate assessment of the gastric emptying rate of a polycarbophil test meal would require a gel particle-specific marker.

In this report we have described a method for the labeling of viscous, homogeneous gel meals containing either guar gum or psyllium. A different method was devised for the labeling of nonhomogeneous test meals containing polycarbophil particles. Estimates of the gastric emptying times for both viscous fiber meals and polycarbophil meals were obtained in dogs.

METHODS

A. Psyllium and Guar Gum

Preparation of the Meal Marker - In preliminary studies, fiber

gels were prepared with saline in which soluble $^{51}CrCl_2$ was first dissolved. However, up to 10% of the soluble isotope migrated from the gel to an adjacent saline phase within one hour. To prevent isotope migration, the soluble label was bound to an insoluble resin.

Carboxymethylethyl-Sephadex (CM-sephadex, Sigma, St. Louis, MO; 120 μ diameter) was prepared by soaking 1 gm of the resin in 50 ml pH 3, 0.9% NaCl (saline) for 48 hours. An aliquot of $^{51}CrCl_2$ (about 0.2 μCi) was then added to the resin-saline mixture and allowed to equilibrate for 24 hours. The labeled resin was then repeatedly washed with acidic saline to demonstrate the stability of the isotope-resin bond in a gastric acid-like mileau. Details of the process are as follows: Aliquots ($\leq$ 0.5 ml, containing approximately 100 mg resin) of the labeled resin slurry were loaded into 10 ml test tubes. Three ml saline was added and the mixture was shaken briefly at 1 and 30 min. At 60 min, the saline wash phase was removed and the resin pellet and the wash were each monitored for gamma radiation (Packard Auto Gamma Spectrometer, Downers Grove, IL). Three ml saline were then added to the resin aliquot and the wash procedure was then repeated. Washes and samples were performed at 60, 120, 180 min and 24 hours. Radioactivity (as counts per minute, cpm) lost to the wash was expressed as (cpm wash/cpm wash + cpm pellet) x 100. Measurements were made on each of 2 samples of the labeled resin. The washing experiment was performed first using pH_1 saline and then with pH_3 saline. The labeled resin was stored at room temperature as a slurry in pH 3 saline. For test purposes, the slurry was stirred and aliquots of the slurry were pipetted as needed. Due to the short

half-life of Cr-51 (28 D), progressively more marker was used per test over the course of the isotope decay period.

Labeling of Guar and Psyllium Suspensions - It was necessary to determine the minimum fiber concentration required to suspend the labeled resin. Suspensions of psyllium (1.0 and 2.0% w/v) (gift from G. D. Searle and Co., Skokie, IL) and guar gum (0.5 and 1.0% w/v) (Chemical Dynamics Corp., South Plainfield, NJ) were each prepared by blending (Oster, low speed x 5 sec) the fiber with 300 ml pH 3 saline to which an aliquot (0.1-0.5 ml) of labeled CM-Sephadex had been added. In general, sufficient resin was added to provide 2000-8000 cpm/gm dried effluent. To simulate the conditions of meal administration in the dog (vide infra), the suspensions were mixed and drawn into 50 ml syringes; after 60 min, the syringes were emptied into 300 ml beakers. To demonstrate uniform distribution of the resin in the suspension, 2 ml samples of the meal were taken at 0 and 3 hours from the top, middle, and bottom portions of the suspension through polyethylene tubes (i.d.: 4 mm, o.d.: 6 mm) that had previously been secured to the inside of the beaker. At each level, the radioactivity per sample at 3 hours was expressed as a percent of the original sample activity. Each fiber concentration was tested in triplicate. The percentages of activity remaining in each layer at 3 hours were compared in a two-way analysis of variance (replicates vs. sample location). Since the distribution of the marker among the layers of each suspension at time 0 was uniform (± 5%), main-

tenance of the original sample radioactivity in each meal portion was taken as a uniform distribution of the resin throughout the entire meal.

Meal Preparation - Meals of 300 ml guar (1.5%) and psyllium (3%) were prepared using pH 5 saline. An aliquot (< 1 ml) of ^{51}Cr-CM-Sephadex was added to the saline prior to blending. After blending, the meals were immediately loaded into 50 ml syringes. Syringe loading was easiest before the fiber gels achieved maximum viscosity (about 5-15 min). An aliquot of the test meal was taken and dried (18 h at 110°C) for determination of the radioactivity as cpm per gram of test meal. Since the total solids content of the meal was known (gm fiber plus gm NaCl), the total activity of the original test meal was calculated as: (cpm/gm dried aliquot) (gm solids in original meal).

Gastric Emptying of Psyllium and Guar Test Meals - Four dogs of mixed breed (10-15 kg) were each surgically fitted with a stainless steel T-shaped cannula which was placed in the duodenum ca 20 cm caudad to the gastroduodenal junction. Surgery was performed using pentobarbital anesthesia 30 mg/kg, iv (Abbott Lab, Chicago, IL) and standard aseptic technique. The details of cannula construction have been published (14). Insertion of a beveled tube into the exteriorized portion of the T-shaped cannula allowed complete diversion of the test meal from the intestinal tract (14). All gastric emptying tests were performed after a two-week surgical recovery period.

The dog was allowed water but no food for 18 hours prior to testing. The meal was administered via an oral-gastric tube. As the meal emptied from the stomach, it drained continuously from the duodenal can-

nula into collecting flasks. Effluent was collected at 5, 10, 15, 30, 45, and 60 min intervals after meal administration. Effluent portions were each dried at 100°C for 18 hours and weighed. The total radioactivity (cpm) recovered was calculated at each collection time. Each meal was tested 2 to 3 times per dog, and only one test was performed per day.

Gastric emptying rates of liquids have been reported as half emptying times, i.e., the time required to empty half of the test meal from the stomach (1). While this term does not relate the pattern or completeness of emptying, it does provide an overall index of the rate of emptying of the meal. In the present studies, the half-emptying times of the meals were derived in two ways. First, the radioactivity collected per interval was expressed as a percentage of the total activity of the meal given. The cumulative percent recovered was plotted against time. The time to recover half of the radioactivity represented the half-emptying time of the meal. Second, the gastric emptying of the meal was based on the cumulative recovery of effluent solids recovered with time (dry weight basis). Differences in the average $E^1/_2$ values when based on effluent solids and effluent radioactivity were assessed with a t test for paried values. Comparisons were performed for both psyllium and guar meals.

The addition of water to gels can reduce their viscosity. Reductions in gel viscosity <u>in vivo</u> due to dilution by gut secretions could cause a concentration of the resin marker in a particular gel fraction. A settling of the marker would be reflected by an elevation of the

radioactivity per gram duodenal effluent relative to the original meal (i.e., a ratio value greater than 1.0). To detect such a concentration of marker, the mean ratio of cpm/gm effluent-to-cpm/gm original meal was calculated based on each individual value obtained at each collection interval for each of the gastric emptying tests performed.

B. Polycarbophil

Labeling of the Polymer - It was observed that unlike psyllium and guar gum, meals of polycarbophil quickly separate into 2 phases. The polymer hydrates to form gel particles which then settle; the unassociated water may be decanted. Such a gel preparation would not suspend insoluble materials. Therefore a gel particle-specific marker was devised. To demonstrate labeling of the hydrated polycarbophil particle, 20 gm sodium polycarbophil granules (gift from A. H. Robins Co., Richmond, VA) were mixed with 500 ml saline in which about 0.1 μCi $Na_2{}^{51}CrO_4$ had been dissolved. The radioactive chromate anion (as $Na_2{}^{51}CrO_4$, New England Nuclear, Boston, MA) was chosen as the meal marker because preliminary studies showed that the cationic form of the isotope (as $^{51}CrCl_2$) could be washed from the gel particles. The polycarbophil-saline mixture was stirred for 1 hour. The hydrated polymer was then separated from unabsorbed saline by filtration through gauze. The gel was recovered and an aliquot of the gel was taken, dried and monitored for radioactivity. The balance of the gel was combined with 300 ml (nonradioactive) saline, and the washing-sampling process was repeated at 1, 2, 4, 6, 8 and 10 hours after initial hydration. The

initial radioactivity per gram of dried polymer was calculated, and the radioactivity per gm polycarbophil (dry weight) remaining after each rinse was expressed as a percentage of the activity originally associated with the polymer. Rinsing experiments were done using pH 2 saline. These experiments were also done using pH 6 saline. Experiments at each pH were done in triplicate. The effect of repeated washing of the labeled polycarbophil particles at different pHs was assessed using a 3-level factorial design analysis of variance (pH vs rinses vs replicates; 15).

Meal Preparation - Preliminary studies revealed that 2 one-hour rinses of the labeled polycarbophil gel was not followed by further isotope loss on rinsing. Thus after sufficient rinsing, 7.0 gm polycarbophil gel was brought to 300 ml with pH 5 saline. The total meal radioactivity was calculated as: cpm/gm gel sample x gm gel used in meal (wet weight basis). The 7.0 gm hydrated polycarbophil aliquot yielded approximately 1.0 gm after drying. Thus, 1.0 gm polycarbophil plus 2.7 gm NaCl (the approximate contribution of 300 ml saline vehicle) equalling 3.7 gm total solids was used as the total meal solids control.

Gastric Emptying - The meal was administered on 2 occasions, and the meal half-emptying times were each determined as for the guar gum and psyllium meals. Because of slow gastric emptying, meal collection was performed for 90 min.

RESULTS

A. Psyllium and Guar

Meal Marker - Chromium-51 (as $^{51}CrCl_2$) remained bound to the CM-Sephadex resin despite repeated washing at pH 1 and 3. Over the 24 h test period, the percent radioactivity appearing in each of the washes never reached 1% of the resin aliquot radioactivity.

Labeling of Psyllium and Guar Suspensions - ^{51}Cr-CM-Sephadex remained uniformly distributed throughout the 1% guar and 2% psyllium suspensions, but not the less concentrated ones (0.3% guar, 1% psyllium). Initial levels of radioactivity among the top, middle and bottom sampling sites were similar (± 5%). No settling of the marker occurred since even after 3 hours, portions taken from each sampling site (top, middle and bottom) each exhibited full radioactivity, relative to control (guar: 94 ± 4, 94 ± 2, and 101 ± 6; psyllium: 92 ± 14, 127 ± 18, and 120 ± 8, % original activity ± SEM; top, middle, and bottom levels, respectively, $p > .05$). Since the $E^1/_2$s of guar (1.5%) and psyllium (3%) meals did not exceed 1 hour (vide infra), maintenance of a uniform distribution of marker for 3 hours in vitro indicated that the resin could remain suspended during the emptying time of the meal.

Gastric Emptying of Psyllium and Guar Meals - The resin-bound marker did not settle out of the meal suspension in vivo. The ratio of the radioactivity per gram dried duodenal effluent relative to that of the original meal averaged less than 1.0 for both psyllium and guar meals (psyllium: 0.83 ± .03, 8 trials in 4 dogs; guar: 0.79 ± .04, 9 trials in 4 dogs). Dilution of the guar meal was revealed at 60 min by

Table 1

Effect of succesive saline rinses on the radioactivity per gram polycarbophil gel.

		Time of Sample (Hours)[a]						
pH	Replicate	0[b]	1	2	4	6	8	10
2	1	100	91[c]	74	83	76	78	75
	2	100	87	82	69	75	69	77
	3	100	83	81	76	70	67	66
	$\bar{X}$	100	87	79	76	74	71	73
6	1	100	96	83	86	84	85	83
	2	100	96	92	87	86	84	82
	3	100	79	83	84	74	63	75
	$\bar{X}$	100	90	86	86	81	77	80

a) sampling separated by continuous washing with saline

b) control value, represents cpm/gm gel after initial hydration

c) % radioactivity remaining per gram gel, relative to control

Means not underlined by a common line are different ($p < .05$) Duncan's multiple range test.

FIGURE 1.

Duodenal recovery of psyllium (3%) and guar gum (1.5%) test meals over the 60 min test time. Abscissa: collection times; ordinate: cumulative percent meal recovered. Psyllium is depicted with circles, guar with triangles. Recovery is based on effluent solids collected (closed points) and effluent radioactivity recovered from the duodenal cannula (open points). For guar, meal half-emptying times ($E_{\frac{1}{2}}$) were slightly but significantly different when based on effluent solids and isotope (30 $\pm$ 5 vs. 34 $\pm$ 4 min, $p < .05$, t test for paired values). For psyllium meals, $E_{\frac{1}{2}}$ values based on effluent solids and isotope were not different (38 $\pm$ 7 vs. 40 $\pm$ 7 min, $p > .05$). Bracket denotes largest SEM for the $E_{\frac{1}{2}}$ values. Note that each plotted point represents the mean of observations from 4 dogs (2-3 obs./dog). The mean $E_{\frac{1}{2}}$ values so obtained differed slightly from mean $E_{\frac{1}{2}}$ values (among dogs) which were generated in the statistical analysis (i.e grand mean of individually plotted $E_{\frac{1}{2}}$ values).

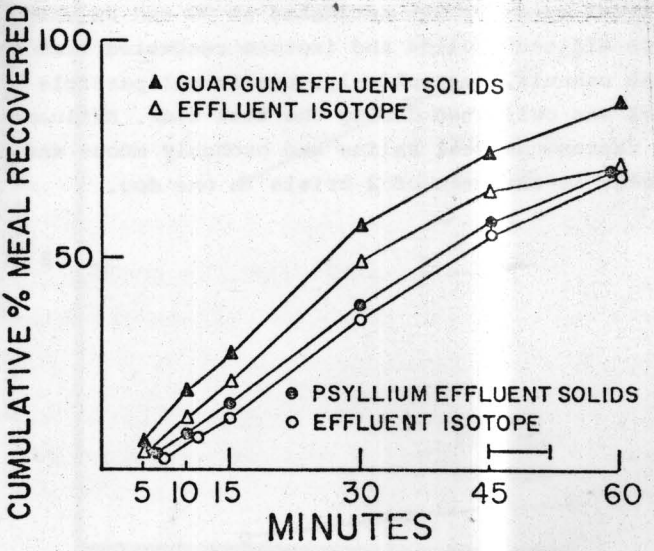
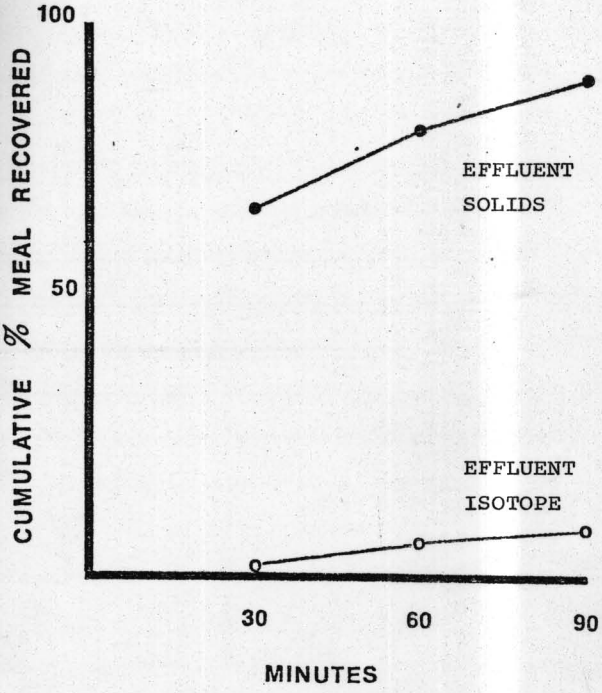

CUMULATIVE % MEAL RECOVERED
100
50
▲ GUARGUM EFFLUENT SOLIDS
△ EFFLUENT ISOTOPE
● PSYLLIUM EFFLUENT SOLIDS
○ EFFLUENT ISOTOPE
5 10 15 30 45 60
MINUTES

FIGURE 2.

Duodenal recovery of the polycarbophil test meal over the 90 min test time. Abscissa and ordinates as in figure 1. Meal half-emptying times are not considered here. At 1.5 hours, meal recovery was estimated at 90 and 8% when based on effluent solids and isotope recovered from the duodenal cannula, respectively. Little gel particle material was collected during the test time. Effluent solids represents meal saline and probably mucus and cells. Each point is the mean of 2 trials in one dog.


100
50
CUMULATIVE % MEAL RECOVERED
EFFLUENT
SOLIDS
EFFLUENT
ISOTOPE
30
60
90
MINUTES

the recovery of duodenal effluent equivalent to 90% of the meal solids, but only 71% of the meal isotope (Fig. 1). This dilution effect was common and probably represented the gastric emptying of gel portions plus gastric and duodenal secretions. In addition, when duodenal effluent was examined for viscosity, the 3% psyllium and 1.5% guar meal effluents each exhibited sufficient viscosity to suspend the resin (vide infra, pp. 248).

Despite incorporation of secretions with the duodenal effluent collected, the meal $E^1/_2$ values based on isotope did not differ much from $E^1/_2$ values based on effluent solids. For guar meals, the mean $E^1/_2$ based on solids was slightly but significantly shorter than when based on isotope collected (30 ± 5 vs 34 ± 4 min, $p < 0.5$, $n = 4$ dogs, 1-3 obs/dog). The $E^1/_2$ values for the psyllium meal were similar when based on effluent solids and isotope (38 ± 7 vs 40 ± 7 min, $p > 0.5$, $n = 4$ dogs, 1-3 obs/dog) (figure 1).

B. Polycarbophil

Labeling of Polycarbophil Particles - At both pH 2 and 6, the first 2 rinses of polycarbophil significantly reduced the radioactivity per gram gel. However, subsequent rinses did not further reduce radioactivity (table 1). Because the labeled gel was thoroughly mixed during washes, the constancy of radioactivity after the third and subsequent rinses also revealed a uniform labeling of the gel (table 1).

Gastric Emptying of Polycarbophil - Polycarbophil emptied from the stomach more slowly than psyllium and guar meals (vide infra). Three

lines of evidence indirectly confirm that Cr-51 faithfully represented the movement of the gel particles. First, the unlabeled water phase of the polycarbophil meal was observed to separate from the gel phase *in vivo* and empty before the gel. This conforms to the usual gastric emptying pattern in dogs and man in which the liquid portion of a mixed meal empties before the solid portion (2). The chromium label was not washed from the gel particles *in vivo* since no radioactivity was recovered with the liquid phase of the meal which was collected from 0-30 min (fig. 2). Secondly, polycarbophil particles have a distinctive appearance in both the hydrated and dried form. The effluent collected over the 90 min test period was mainly the meal saline phase; only a small amount of gel particles (relative to the amount administered) was observed. Finally, in other studies (*vide infra* pp. 227) dogs were fed 90 gm labeled polycarbophil and sacrificed 4 hours later. Meal gel was recovered from the stomach and intestines by scraping the mucosa. Ninety percent (range 85-97%, n = 4 dogs) of the isotope was recovered. Importantly, isotope was never recovered in the absence of gel particles. These data help verify that the isotope was a true marker for the gel.

Polycarbophil emptied quite slowly ($E^1/_2$ > 1.5 h.) relative to psyllium or guar. As with the recovery curves for psyllium and guar, the curve depicting the recovery of labeled polycarbophil was situated to the right of and below the effluent solids-recovered curve (fig. 2). This suggests a significant contribution of nonmeal solids (cells, mucus, salt) to the recovered effluent. Specifically, at 90 min, the

equivalent of 90% of the solids (3.33 gm) was recovered. Based on isotope recovery, only 8% of the polycarbophil was recovered, accounting for 0.08 gm of the solids at 90 min. NaCl could not have contributed more than the 2.7 gm used in the original meal. Thus salt (2.7 gm) plus polycarbophil (0.08 gm) combined to account for only 75% (2.78/3.33 gm) of the solids at 90 min. Cells and mucus likely accounted for the remaining 15%. The low total recovery of the gel (8%) over the 90 min collection period is consistent with other studies that show that polycarbophil empties slowly from the stomach.

DISCUSSION

^{51}Cr-CM-Sephadex faithfully represented the movement of the guar and psyllium meals *in vivo*. *In vitro*, the isotope was bound to an insoluble resin and this association was unaffected by washing. This result suggests that the marker would not diffuse from the gel to gut secretions *in vivo*. In addition, the resin-bound isotope was well suspended at the fiber concentrations employed. The gastric mixing associated with gastric emptying presumably aided in maintaining the suspension *in vivo*. That guar (1.5%) and psyllium (3%) test meals remain sufficiently viscous to suspend the resin even after passage through the duodenal cannula is documented elsewhere (*vide infra*, pp. 248). Naturally, test meals that do not suspend the ^{51}Cr-CM-Sephadex would not be adequately labeled for the purposes of measuring half-emptying times. Water-soluble markers such as phenol red, Cr-51 and ^{14}C-PEG-4000 are uniformly distributed throughout the water phase of aqueous meals (1).

Such markers may be useful for studies of the gastric emptying of fiber meals of low viscosity, although there is no evidence that they will specifically measure the insoluble fraction of such meals. Despite this possible shortcoming, effluent solids- and effluent isotope-collected curves for low viscosity meals of psyllium and guar are essentially superimposable (not shown). Since the collection times for these meals are brief (ca 10-15 min, vide infra pp. 159), it is unlikely that secretions confound the estimates of their half-emptying times. Thus soluble markers are probably acceptable tools for the accurate estimate of the half-emptying time of such meals.

Although ^{51}Cr-CM-Sephadex is an adequate marker for the fiber test meals, it is probably more accurate for measuring meal $E^1/_2$ than the total emptying time. Approximately 60-70% of the guar and psyllium meals emptied during the 60 min test time and most of the balance of the meal emptied by 2 hours (not shown). Whether the small amount of meal remaining (20-30%) after 60 min is diluted by secretions or remains sufficiently viscous to suspend the resin marker is unknown.

The minimal dilution of the fiber meals during their 30-40 min half-emptying times was highlighted by the similarity of the effluent solids- and the effluent isotope-recovery curves. As a result, fiber meal half-emptying times can be adequately estimated when based on effluent solids alone. In contrast, for the more slowly emptying polycarbophil particles, the particle-specific label was essential for estimating $E^1/_2$. However, as a result of polycarbophil particle-

specific labeling, both meal half- and total emptying times may be measured accurately.

Polycarbophil was easily and effectively labeled with Cromium-51. After initial rinses, the gel-isotope bond was stable in an acid mileau for at least 8 hours _in vitro_ (about twice the half-emptying time for a 90 gm polycarbophil meal, _vide infra_ pp. 194). _In vivo_, the saline phase of the polycarbophil meal emptied rapidly (within about 10 min) but was not radioactive; the radioactive gel particles remained in the stomach for subsequent emptying. Finally, 4 hours after ingestion of radioactive polycarbophil, essentially all of the radioactivity could be recovered from the gut but was never recovered in the absence of the gel. Such observations support the ability of Cr-51 (as the cromate anion) to remain bound to polycarbophil _in vivo_ and act as a marker for the gel particles. The labeling of the gel proper is important since a) meal water emptied rapidly and separately from the gel, and b) a significant percentage of nonmeal solids were added to the test meal over the 1.5-hour collection time. In preliminary studies, the diameter of cannulas implanted into the duodenum has been shown to greatly influence the emptying rate and degree of meal dilution. Irrespective of collection technique, since the gel particle is specifically labeled, the use of isotope instead of solids to calculate recovery prevents gross underestimates of the half-emptying time of the polycarbophil test meals.

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CHAPTER 3

Canine Gastric Emptying of Fiber Meals: Influence of Meal Flow Properties and Antroduodenal Contractile Activity.

ABSTRACT

The influences of meal viscosity and antroduodenal contractile activity on the gastric emptying of fiber meals containing guar gum and psyllium were investigated. Four dogs were each surgically prepared with strain-gage force transducers on the gastric antrum and orad duodenum. In each dog, a T-shaped cannula was implanted into the mid-duodenum. After recovery, increasingly viscous fiber meals were administered via an oral-gastric tube. Rate of gastric emptying was based on the recovery of 50% of an isotopic meal marker with time. The antroduodenal motor responses to and the half-emptying times ($E^1/_2$) of the test meals were each assessed relative to saline. In addition, meal viscosities were examined over a wide range of shear rates using a rotational viscometer. The patterns of change in the viscosity:shear rate relation were studied for each meal to reveal the shortcomings of single point viscosity measurements as predictors of the gastric emptying rates of different fiber types.

Low viscosity guar and psyllium meals each exhibited half-emptying times and emptying curves similar to those of saline ($E^1/_2$ = 10 min). In contrast, high viscosity guar and psyllium meals emptied more slowly than low viscosity meals and exhibited nearly the same $E^1/_2$ (ca 40 min). Viscosity studies showed that psyllium and guar exhibited markedly different viscosity:shear rate relationships. Despite similar $E^1/_2$'s, the highest concentration of guar was 2-fold more viscous than psyllium at 150 rpm. Antroduodenal contractile responses to the meals were neither significant nor concentration dependent.

We conclude: a) antroduodenal motor activity is not a regulator of the gastric emptying of fiber meals; and b) guar and psyllium meals each display viscosity-related delays in gastric emptying time, but because fiber meals can exhibit different viscosity:shear rate relations, single viscosity values are not necessarily predictive of the gastric emptying rates of different fiber meal types.

KEY WORDS

Key Words: dietary fiber, gastrointestinal motility, gastric emptying

INTRODUCTION

Dietary fiber has recently received much attention as an adjunct in the treatment of certain endocrine disorders (15,16,23,25,29,31). Specifically, dietary supplementation with fiber sources such as guar gum (commercial food thickener) and psyllium (bulk forming laxative) has resulted in significantly improved control of postprandial glycemia in diabetics (16,23,25,31). This beneficial effect is thought to be derived, in part, from a delayed gastric emptying of meal carbohydrates (13,16), although this hypothesis has not been extensively or rigorously tested.

Dietary fibers can exhibit markedly different physical properties as part of a test meal. For example, alpha cellulose empties from the stomach as fibrous particles (20). In contrast, aqueous meals containing guar or psyllium empty as homogeneous gels (26). Differences in the patterns of gastric emptying of particulate or gel-forming fibers alone have not been studied. Such information would establish the importance of physical differences to the gastric emptying of different fibers and help predict how fibers would influence the emptying of conventional liquids and solids.

Increases in viscosity have only recently been associated with a delay in the gastric emptying of test meals (11). Since many fibers can thicken liquids and since nearly all ingesta empties from the stomach in a fluidized form, viscosity probably also figures importantly in the gastric emptying rate of meals with fiber added. Liquid meal viscosity may be assessed using a rotational viscometer. The meal sample is

loaded into a cup and then subjected to the frictional forces of a rotating spindle which produces a controlled rate of flow, or shear. The viscosity, or tendency of the liquid to resist flow, is documented over a range of shear rates. In general, 2 types of flow will be revealed. Newtonian flow is exhibited by water and is characterized by a shear rate-independent viscosity value. In contrast, non-Newtonian flow presents with a shear rate-dependent viscosity pattern. For example, when meal water is combined with fibers such as guar gum, pectin, and psyllium, gel-like mixtures form. Flow is initiated upon sufficient shear, and meal viscosity then increases, decreases or plateaus with further increases in shear rate (7). For such non-Newtonian mixtures, it follows that single viscosity values obtained at specified shear rates are not predictive of overall shear rate:viscosity relations. Thus two test meals with the same viscosity can exhibit vastly different viscosities upon shear, i.e., during gastric mixing. Similarly, meals of initially different viscosities could exhibit similar viscosities upon gastric mixing. The viscosity of a gel-forming fiber test meal probably influences its rate of gastric emptying. However, single estimates of viscosity may not help predict the gastric emptying rates of meals characterized by differing viscosity:shear rate patterns.

The orad small intestine plays a significant role in the orderly emptying of liquids from the stomach (3,10,15,30). In contrast, the gastric antrum is critical to the particle size reduction of solids, and general gastric continence (18,21,22). Postprandial motility is marked by coordinated antral and duodenal contractile activity (1). This ac-

tivity creates an intraluminal pressure gradient which intimately influences gastric emptying. Rapidly emptying meals are accompanied by an antral-to-duodenal gradient. Reversal of this gradient accompanies a delayed gastric emptying of liquid meals containing fatty acids (30). As with the addition of fatty acids, increases in meal viscosity are associated with slowed emptying (11). Whether progressive reversals of the antroduodenal contractile gradient accompany, and possibly regulate, the gastric emptying of increasingly viscous meals has not been investigated.

These studies were performed to a) characterize the gastric emptying of increasingly viscous meals containing the dietary fibers guar gum, and psyllium, b) determine whether antroduodenal contractile gradient changes accompanied the different rates of emptying of the increasingly viscous fiber meals, and c) relate the importance of meal viscosity: shear rate relations to the gastric emptying rates of different types of non-Newtonian fiber meals. Our results suggest that meal flow properties, rather than motility, are the major determinants of the gastric emptying times of viscous fiber test meals.

MATERIALS AND METHODS

Surgical Model - Four dogs of mixed breed (10-15 Kg) were each prepared with strain-gage force transducers and mid-duodenal cannulas using aseptic surgical technique. Dogs were each anesthetized with pentobarbital 30 mg/kg, i.v. (Abbott Lab, Chicago, IL). At surgery, 4 strain-gage force transducers were implanted in the transverse axis of the stomach and orad duodenum. The units were situated 6 and 3 cm orad and 6 and 9 cm caudad to the gastroduodenal junction. These units were employed for chronic detection of spontaneous and test meal-induced circular muscle contractions. The fabrication and method of implantation of these units have been described (2). In addition, a T-shaped stainless steel cannula, similar to that described by Komarek (19), was implanted into the duodenum approximately 25 cm caudad to the gastroduodenal junction. The tubular base of the cannula fitted snugly into the lumen of the mid-duodenum. The cannula was constructed of stainless steel tubing (i.d. 1 cm, o.d. 1.2 cm). The base measured 3.2 cm in length, and the cannula barrel extended 5 cm from the base. The cannula barrel was exteriorized through a stab wound made lateral to the midline and below the last rib. During the experiments, a tubular insert cut to 45° at one end was inserted into the cannula barrel to permit diversion and subsequent collection of duodenal effluent. A 2-week recovery period was allowed before testing.

Test Meals - Two types of fiber, milled psyllium seed (G. D. Searle & Co., Skokie, IL) and guar gum (Chemical Dynamics Corp., South Plainfield, NJ), were studied. Meals of psyllium (1.0 and 3.0%) and

guar gum (0.3, 1.0, and 1.5%) were each prepared by blending the dry fiber with 0.9% NaCl (saline). The maximum meal fiber concentrations used were established by the difficulty with which they passed through an oral-gastric tube. All meals measured 300 ml total. A saline meal served as the control. Low viscosity meals (psyllium 1%, guar 0.3%) were labeled by dissolving the gamma emitter $^{51}Na_2CrO_4$ in the meal saline prior to blending. The thicker meals (psyllium 3%, guar 1.0 and 1.5%) were each labeled by suspending an insoluble radioactive marker (^{51}Cr-carboxymethylethyl-Sephadex) in the fiber meal. The rationale and method for labeling of sufficiently viscous fiber meals with ^{51}Cr-Sephadex for assessment of gastric emptying time has been reported (26). Each meal presented as a homogeneous gel mixture and demonstrated concentration-dependent increases in viscosity (vide infra). Meal fiber concentrations included those used clinically (body weight basis) or commercially (% w/v).

Markedly hypo- and hyperosmotic liquids empty from the stomach more slowly than isosmotic liquids (15). The effect of fiber on saline vehicle osmolarity was determined by the freezing point depression method (Precision Instruments, Waltham, MA). The osmolarity of 1% guar and 3% psyllium gels closely approximated that of the 0.9% saline vehicle (mean ± SEM: 283 ± 3 mOsm/L, range 270-292 mOsm/L, 3 obs/preparation).

Gastric Emptying Studies - The effect of meal fiber concentration on the rate of test-meal emptying was determined. Dogs had access to water but not food for 18 hours prior to testing. All meals were administered to the dogs via an oral-gastric tube using large volume

syringes. After meal administration, a beveled cannula barrel insert was placed and used to divert the duodenal effluent to a collecting flask. After the administration of guar (0.3%) and saline meals, duodenal effluent was collected at 2, 4, 6, 8, 10, 15 and 30 min. After all other meals, effluent was collected at 5, 10, 15, 30, 45 and 60 min. The effluent portions were dried overnight (110°C x 18 h) and then monitored for the radioactivity recovered at each collection time (Packard Auto Gamma Spectrometer, Downers Grove, IL). For each test, the cumulative percent radioactivity recovered was plotted against time. The time required to recover half of the meal ($E^1/_2$, hereafter referred to as half-emptying time) was read from the graph and used as an index of the rate of gastric emptying. Each fiber type and concentration was administered to the dogs at random and replicated at least twice.

Motility Studies - Canine interdigestive motility patterns are well established (6,8). In the fasted state, 3 major activity phases - 1, 2, and 3 (also termed the basal, preburst, and burst states,) - occur in series. The entire series is repeated approximately every 100 min. Phases 1, 2, and 3 are marked by contractions of low, intermediate, and maximal frequency and amplitude, respectively. Phase 3 is a brief interval (ca 10 min) of maximal amplitude contractions. Antral and duodenal contractile responses may be expressed as a percentage of their respective phase 3 maximums. In the present studies, the test meals were administered after completion of phase 3, i.e., the start of phase

1. The use of phase 1 minimized the contribution of spontaneous motor activity to contractile responses elicited by the test meal.

The antroduodenal contractile activity associated with the $E^1/_2$ of the test meals was quantified. Contractile responses were expressed as a percentage of the maximum contractile activity seen during the pretreatment phase 3 interval. Antral and duodenal motor responses were quantified similarly. First, the postprandial motor responses were indexed. The index was calculated as:

$$\text{weighted index} = \frac{1\ (\#\ \text{contractions, 20-49\%}) + 2\ (\#\ \text{contractions, } \geq 50\%)}{E^1/_2 \text{min}}$$

where response contractions were scored with one point if they measured 20-49% of the pretreatment phase 3 contractile amplitude and 2 points if they met or exceeded 50% of the pretreatment phase 3 amplitude. Dividing the numerator by the $E^1/_2$ (min) yielded the per minute indexed motility value associated with the emptying of the test meal.

In order to compare antral and duodenal contractile responses, the indexed values were then normalized by expressing them as a percent of the maximum possible per minute index value which occurs during the pretreatment phase 3 interval. Antral and duodenal maximums were calculated according to the method for the weighted index. Idealized antral and duodenal maxima were used throughout the analysis. On the average, antral and duodenal phase 3 contractions occur with a frequency of 4.5 and 18 per min, respectively. Since phase 3 contractions are of maximal amplitude, each was scored with 2 points. Thus the maximum per minute

index values for the antrum and duodenum were calculated to be 9 and 36, respectively. The percent maximum response was used in all analyses and was calculated as:

$$\%\ \text{maximum response} = \left(\frac{\text{weighted index value}}{\text{maximum index value}} \right) 100$$

Meals replace fasted state motility with a characteristic antroduodenal motility pattern and variably delay the reappearance of fasted-state motor patterns (1,6). The ability of fiber test meals to interrupt interdigestive motor patterns was characterized. Specifically, measurements were made of a) the antroduodenal motor activity recorded from the time of meal administration until the onset of the post-treatment phase 3 interval (indicating the return of the fasted state) and b) the time of reappearance and the duration of the post-treatment phase 3 interval. In addition, motor activity in response to fiber meals was indexed and compared both with that seen after saline alone and with the spontaneous activity normally seen between phase 3 intervals.

Test Meals: In Vitro Flow Properties - The various psyllium and guar gum test meals exhibited marked differences in viscosity. Viscosity differences could influence meal gastric emptying rates. Therefore, test meal flow properties were characterized using a rotational viscometer (Rotovisco, RV-12 Haake, Inc., NJ). Guar gum (0.3, 1.0, and 1.5%) and psyllium (1.0 and 3%) were each prepared. Because agitation can alter gel viscosity, *in vivo* test conditions were simulated by mixing

the gel and then loading it into large syringes. After 60 min, 40 ml aliquots of the gels were each loaded into bob and cup (MV1K) assemblies and subjected to continually increasing and then decreasing rates of shear (0→300→0 rpm). The shear stresses recorded in response to increasing rates of shear were automatically plotted (Hewlett Packard x-y recorder [Model 7015B]) and viscosity vs. shear rate diagrams were constructed (7,12). The resulting flow patterns were described as pseudoplastic or dilatant. Pseudoplastic flow is marked by initially high and then lower viscosity in response to increasing rates of shear (7). Dilatant flow is marked by increasing viscosity with increasing shear rates (7). Viscosities for the various concentrations of each fiber tested were compared at the arbitrarily chosen half-maximal shear rate (150 rpm). Each fiber concentration was tested in duplicate. In addition, the viscosity of the saline control meal was measured using an Ostwald-Cannon-Fenske capillary viscometer. All measurements were made on samples maintained at 37° C.

Data Analysis - Concentration-related delays in the $E^1/_2$ of fiber meals were detected using a 2-way analysis of variance (ANOVA) (dogs vs. fiber concentrations). Differences in treatment means were identified with Duncan's multiple range test (28).

The influences of fiber concentration, individual dogs, and the recording sites (antrum and duodenum) on the contractile responses to fiber were assessed in a 3-level factorial design ANOVA (28). Analyses were performed for guar (3 dogs) and psyllium (4 dogs). This type of analysis permitted the detection of fiber concentration-related changes

in both antral and duodenal contractile responses. Further, differences between antral and duodenal responses at each fiber concentration, which constituted the contractile gradient, were also identified. Fiber-related changes both in the time of reappearance and in the duration of the post-treatment duodenal phase 3 intervals were assessed using a 2-way ANOVA (dogs vs. fiber concentrations).

RESULTS

Gastric Emptying Studies - The test meals emptied either far more slowly or at the same rate as the saline control. The meals of highest fiber content (psyllium 3% and guar 1.5%) presented as the most viscous gels, exhibited similar $E^1/_2$ values and emptied far more slowly than all other test meals (Table 1, Figures 1 and 2). The low fiber content meals (psyllium 1% and guar 0.3 and 1.0%) each exhibited $E^1/_2$ values and emptying patterns that did not differ from those of the saline control meal (Table 1, Figures 1 and 2).

The gastric emptying of all test meals commenced immediately. There was no initial lag period, even with meals of highest viscosity (psyllium 3%, guar 1.5%) (Fig. 1 and 2). In addition, individual test collection curves always approximated linearity at least until 50% of the meals had emptied.

Test-meal emptying was nearly complete during the test time. Frequently, additional duodenal effluent would be collected during the post-test period, i.e., from 60 minutes until the end of the post-treatment phase 3 motor interval. Total meal recovery averaged 85% for all test meals (range 79-96%).

Motility Studies - The half-emptying times of the fiber meals were not accompanied by increases in antral or duodenal motor activity, relative to control. The duodenal contractile responses were negligible (2-10% of maximum) and not dose related (Figure 3). The antral responses were more marked (17-31% of maximum) but not dose related (Figure 3). Despite this low activity profile, antral activity consistently tended

Table 1. Effect of Meal Fiber Concentration on Its Half-emptying Time (min)

A. Psyllium (% w/v)

Dog	0[a]	1	3	p[b]
1	8[c](2)[d]	8(2)	48(2)	
2	11(2)	17(2)	25(2)	
3	11(4)	15(3)	53(3)	
4	8(4)	11(2)	33(2)	
$\bar{X}$ ± SEM	10 ± 1	13 ± 2	40 ± 7	< .01[e]

B. Guar Gum (% w/v)

Dog	0	0.3	1.0	1.5	
1	8(2)	11(2)	16(2)	37(2)	
2	11(2)	5(1)	7(1)	43(1)	
3	11(4)	20(3)	19(3)	22(3)	
4	8(4)	5(2)	8(3)	33(3)	
$\bar{X}$ ± SEM	10 ± 1	10 ± 4	13 ± 3	34 ± 5	< .01

[a] saline vehicle control
[b] 2-way analysis of variance
[c] mean
[d] number of trials
[e] means not underlined by a common bar are different ($p < .01$) Duncan's multiple range test.

FIGURE 1.

Plot of the cumulative percent psyllium (1 and 3%) recovered from the duodenal cannula over the 60-min test period. Points each represent the mean percent meal recovered from 4 dogs (2-3 obs./dog). Maximum S.E.M. depicted by bar. Saline and psyllium 1% emptied in an exponential pattern while psyllium 3% emptied in a zero-order pattern.

CUMULATIVE % MEAL RECOVERED
100
50
5 10 15 30 45 60
MINUTES
△ SALINE
○ PSYLLIUM 1 %
● PSYLLIUM 3 %

FIGURE 2.

Plot of the cumulative percent guar gum (0.3, 1.0, and 1.5%) recovered from the duodenal cannula over the 60-min test time. Points each represent the mean for 4 dogs (1-4 observations/dog). Maximum S.E.M. depicted by bar. Meals of saline and guar 0.3 and 1.0% emptied in an exponential pattern while guar 1.5% emptied in a zero-order pattern.

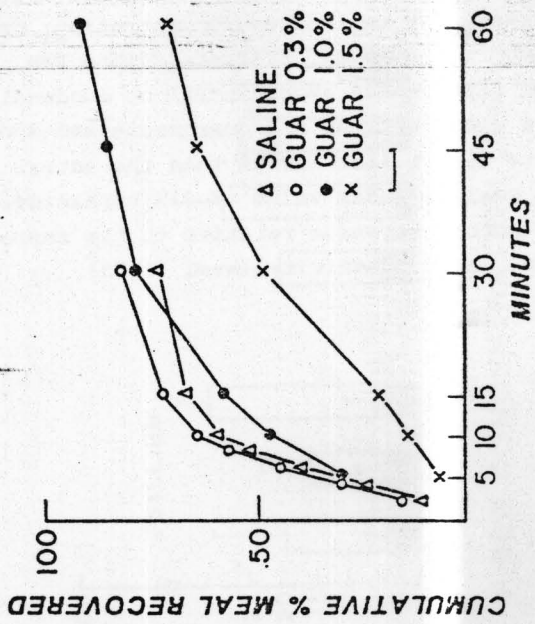

CUMULATIVE % MEAL RECOVERED
100
50
5 10 15 30 45 60
MINUTES
Δ SALINE
o GUAR 0.3%
• GUAR 1.0%
× GUAR 1.5%

FIGURE 3.

Antral (closed bar) and duodenal (open bar) indexed motor activity associated with test meal half-emptying times. Abscissa: test meal fiber concentration; ordinate: percent maximum motor index. Brackets denote SEM. There were no differences among antral or duodenal responses for both psyllium and guar meals and duodenal responses were always less marked than the antral responses. A maximum index value of 31% emphasizes the low grade of the motor responses relative to the respective interdigestive phase 3 activity level (100%).

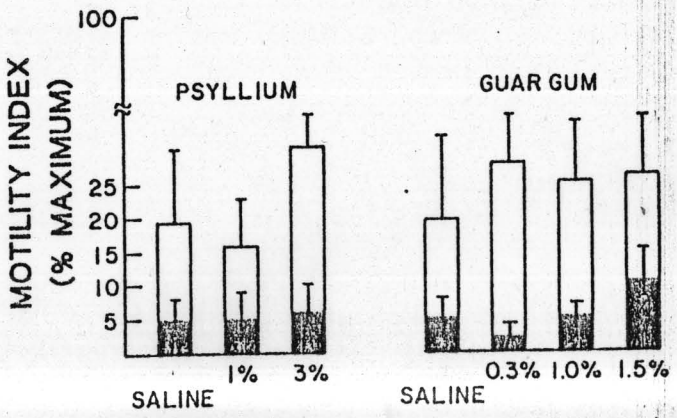

MOTILITY INDEX
(% MAXIMUM)
100
25
20
15
10
5
PSYLLIUM
GUAR GUM
SALINE
1%
3%
SALINE
0.3%
1.0%
1.5%
FIBER CONCENTRATION (%w/v)

Table 2. Effect of Fiber Test Meals on Canine Motility Parameters.

	Treatments						
			Psyllium (% w/v)		Guar Gum (% w/v)		
Motility Parameter	Untreated	Saline	1.0	3.0	0.3	1.0	1.5
A) Motor index from meal until subsequent phase 3 interval (% maximum)[a]							
Antrum	5.5±1.5	8.0±2.4	13.2±5.3	16.9±8.3	12.7±3.6	9.2±0.8	9.6±3.6
Duodenum	8.7±2.5	7.2±1.6	8.5±3	11.1±5.3	6.7±4	10.3±7	7.7±1.8
B) Motility Cycle duration (min)[b]	100 ± 6	101 ± 6	96 ± 14	115 ± 2	102 ± 5	86 ± 15	123 ± 20
C) Phase 3 duration (min)[c]	15 ± 2	17 ± 4	11 ± 2	12 ± 2	12 ± 2	13 ± 2	12 ± 3

[a] n = 4 dogs (psyllium), 3 dogs (guar gum). Values for untreated and saline treatments correspond to psyllium analysis. Values from guar gum analysis were not different and are not shown. Response means compared with a 3-level factorial ANOVA (fiber concentrations vs. recording location vs. dogs). Psyllium and guar analyses performed separately. Analysis revealed no effect of fiber concentration or gage location on antral or duodenal motor responses to fiber test meals.

[b,c] n = 3 dogs, 2-way ANOVA (treatments vs. dogs), $p > .05$.

to exceed that of the duodenum, i.e., an antroduodenal contractile gradient tended to be present after each treatment (Figure 3). In the cases of psyllium (3%) and guar (0.3%) antral activity was significantly higher than duodenal activity ($p < .05$).

The administration of fiber meals did not significantly interrupt ongoing motility cycles of the interdigestive state. No increases in motor activity were recorded from the time of meal administration until the subsequent phase 3 (which included the meal $E^1/_2$), relative to saline and spontaneously occurring activity. Further, the subsequent phase 3 intervals were neither delayed in onset nor changed in length (Table 2). Diversion of gastric effluent from the duodenum plus essentially complete gastric emptying of the meal likely accounted for the undelayed return of the phase 3 interval.

In Vitro Flow Properties - Guar and psyllium each exhibited concentration-dependent increases in meal viscosity but distinctly different flow patterns (Figures 4 and 5). Guar (1.0) and (1.5%) each exhibited pseudoplastic flow; steadily increasing shear rate was accompanied by a rapid decrease in viscosity, which soon plateaued. This pattern results from an initial breakdown of intermolecular electrostatic bonds. Further increases in shear rate do not affect viscosity, i.e., Newtonian-like flow ensues. Subsequent decreases in shear rate (down curve) did not alter this shear rate:viscosity relation (Figure 4). In contrast, guar (0.3%) demonstrated water-like or Newtonian flow; increases and decreases in shear rate did not appreciably affect meal viscosity (Figure 4). Psyllium (3%) exhibited dilatant flow. Viscosity

FIGURE 4.

Effect of steadily increasing shear rate on the viscosity (cp) of guar gum test meals (0.3%: closed triangles; 1.0%: closed circles; 1.5%: open circles). Points are each the mean of 2 observations. Guar 1.0 and 1.5% each exhibit pseudoplastic flow while guar 0.3%, like saline, exhibits Newtonian flow. Return curves are superimposable on the up curves indicating the absence of thixotropy.

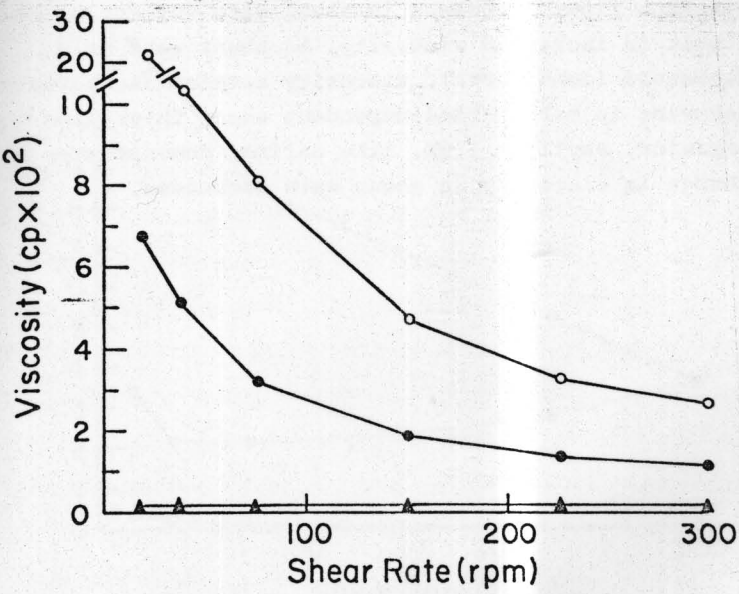
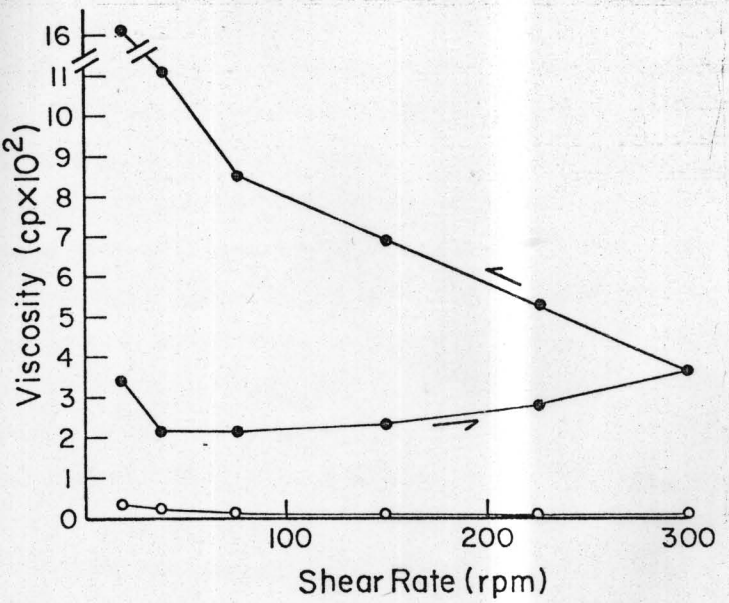

30
20
10
8
6
4
2
0
Viscosity (cp x 10²)
100
200
300
Shear Rate (rpm)

FIGURE 5.

Effect of steadily increasing shear rate on the viscosity (cp) of psyllium 1.0% (open circles) and 3.0% (closed circles) test meals. Points are each the mean of 2 observations. Psyllium 3% exhibits dilatant flow. Increases in shear rate (up curve) result in increased viscosity. As shear rate is decreased (down curve), viscosity remains high. Such behavior is termed time-dependent shear thickening behavior. Psyllium 1.0%, like saline, demonstrates no change in viscosity as shear rate increases.


16
11
10
9
8
7
6
5
4
3
2
1
0
Viscosity (cp×10²)
100
200
300
Shear Rate (rpm)

increased with increasing rates of shear (Figure 5). Dilitant flow results when the water which surrounds the psyllium macromolecule is forced (by shear) away from the intermolecular spaces. An elongation of the polymer strand plus an increased intermolecular friction is thought to account for increased viscosity (7). Subsequent reductions in shear rate resulted in further increases in viscosity (Figure 5). Failure of the return curve to coincide with the up curve revealed thixotropy. This phenomenon refers to the time-dependent return of the elongated psyllium molecule to its original shape and intermolecular hydration state (7). Psyllium (1%), like guar (0.3%), displayed near-Newtonian flow with a low viscosity, relative to the 3% psyllium meal.

Guar and psyllium meals each exhibited concentration-dependent increases in viscosity over the range of shear rates tested.. At half-maximal shear rate (150 rpm), guar 0.3, 1.0 and 1.5% exhibited viscosities of 13, 193 and 476 cp, respectively (Figure 4). Psyllium 1% and 3% exhibited viscosities of 12 and 235 cp (as per up curve), respectively (Figure 5).

Despite a wide range of viscosities, the test meals emptied with one of two half-emptying times. Over a range of 1-193 cp (@ 150 rpm), meals of guar (0.3 and 1.0%) and psyllium (1%) emptied at the same rate as the saline control. Similarly, meals of psyllium (3%) and guar (1.5%) both exhibited $E^1/_2$ of approximately 40 minutes despite viscosities of 235 and 476 cp, respectively (@ 150 rpm).

DISCUSSION

Progressive increases in meal fiber concentration resulted in the delayed emptying of test meals. Possible mechanisms for this delay of emptying include a) a recruitment of duodenal control factors by test meal chemical properties, b) concentration-dependent changes in meal flow properties, and c) a concentration-dependent reversal of the antro-duodenal motor gradient. Liquid meal emptying time is predictably delayed by the addition of fatty acid (oleate, 14,30) or amino acids (esp Phe, 10), and by increasing the meal osmolarity (14). This effect is postulated to be mediated by small intestinal epithelial receptors (14). In the case of oleate, this stimulation is transduced into a reversal of the usual antrum-to-duodenum contractile gradient which accompanies a delayed gastric emptying (30). However, neither guar nor psyllium (nor any other dietary fiber) is degraded to its constituent sugars in the stomach or upper small intestine (29), and the addition of these carbohydrate macromolecules to the meal saline does not alter meal osmolarity. Thus fiber-induced stimulation of orad intestinal "receptors" is an unlikely mechanism for the delay in the gastric emptying of high concentration fiber test meals.

The gastric emptying of digestible solids is slower than that for liquids mainly because solids must undergo particle size reduction to less than ca 2 mm diameter prior to emptying (21). However, particle size reduction is not necessary for smooth, homogeneous gels of guar and psyllium. Nonetheless, the more viscous meals of guar and psyllium emptied slowly. In the absence of intestinal stimulation or the need for

particle size reduction, meal flow properties such as viscosity emerge as a possible influence on gastric emptying rate.

The present studies, and recent studies of potato meal emptying (11), document increasingly delayed gastric emptying as test meals increase in viscosity. The present studies also show that meal viscosity is not necessarily even generally predictive of the gastric emptying rates of meals of different fiber types. Marked viscosity differences between psyllium and guar meals were not paralleled by emptying time differences. This was demonstrated by the similar half-emptying times (ca 40 min) of meals containing psyllium (3%) and guar (1.5%) despite a 2-fold difference in their viscosities (psyllium, 235 cp vs. guar, 476 cp, @ 150 rpm). This effect is highlighted by Ehrlein and Prove's (11) report of a half-emptying time of ca 40 min for potato meals of 10^6 cp. The lack of association of meal viscosity with emptying time among fiber types suggests that the overall flow pattern of a meal is probably more important to its emptying rate than a single estimate of viscosity.

Differences in meal flow properties could account for the similar $E^1/_2$ for the most viscous psyllium and guar meals. Psyllium exhibited dilatant flow while guar exhibited pseudoplastic flow. Although psyllium (3%) was half as viscous as guar (1.5%) at 150 rpm, their similar emptying rates probably reflected the combined effects of psyllium's tendency to become more viscous and guar's tendency to become less viscous with agitation (shear). The range of psyllium-to-guar viscosity ratios of 1:4 at 75 rpm, to about 1.4:1 at 300 rpm illustrates this

effect. Presumably, gastric and duodenal mixing acted to agitate the meals, although precisely how shear *in vitro* compares to the shear caused by even nominal gastric mixing is unknown.

Little is known of the effects of various gel-forming dietary fibers on the gastric emptying of liquids. Using small amounts of the fiber pectin to thicken his meals, Hunt (14) dismissed modest increases in meal viscosity as having an influence on the emptying of liquids. Subsequently, the addition of fiber (psyllium 3%, guar gum 4%) to liquid carbohydrate meals was found to delay gastric emptying and cause attentuations of postprandial serum glucose elevations (13,16,31). Two major mechanisms account for the effect of fiber on postprandial glycemia. First, certain fiber types impair the intestinal absorption of glucose (4,17). Secondly, fiber delays liquid emptying (13). The present studies establish that fiber-delayed emptying is related to the meal fiber concentration employed.

Gastroduodenal motor gradients are not regulators of the emptying time of fiber meals. Neither guar nor psyllium elicited significant amounts of antral or duodenal contractile activity, relative to saline. These results conflict with those of the only other published report in which the relation between gastric motility and the gastric emptying of viscous meals was examined (24). Prove and Ehrlein (24) examined the gastric motor responses to increasingly viscous potato meals. Using induction coils, which measured the extraluminal diameter of the gastric antrum during contraction, decreasing but almost imperceptible degrees of antral contraction (indentation at fluoroscopy) were related to the

gastric emptying of increasingly viscous potato meals. As in the present study, there was no relation between meal viscosity and antral contractile activity when measured by strain-gage force transducers. However, serosal gages and coils provide essentially the same information. Transducers monitor muscle contraction; coils monitor the result of contraction, i.e., organ deformation. Two points seriously weaken an argument for a relation between the degree of antral "indentation" and the gastric emptying of viscous meals. First, antral indentation was not measured with reference to a contractile event known to promote gastric emptying. No recording of interdigestive phase 2 or 3 antral indentation or even of postprandial indentation was employed as a control. Fluoroscopy reveals that phase 3 contractions occlude the antral lumen (9,27). The slight (1.2 mm) difference in maximum antral indentation reported after medium and low viscosity potato meals, while statistically significant, is likely to be functionally inconsequential. Secondly, antral contractions (indentations) are probably not requisite to low viscosity meal emptying since antrectomy is not disruptive to this process (32) and since antral contractions are often absent in the presence of liquid emptying. These arguments and the present studies suggest that the gastric (and gastroduodenal) motor profile does not influence fiber meal emptying.

As an alternative to a regulatory role for antroduodenal activity, tonal changes of the gastric body could influence the rate of fiber meal gastric emptying. Intragastric volume is determined largely by the degree of gastric body distention. The importance of an intact gastric

body for the accommodation to liquid volume and the unhurried emptying of liquids is well established (18). In the present studies fiber gels may simply be behaving like thick liquids whose emptying is governed by changes in intragastric pressure. In the absence of a marked antroduodenal contractile gradient, meal flow properties and tonal changes of the gastric body might then be major influences on the evacuation of these viscous meals from the stomach.

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CHAPTER 4

Canine Gastric Emptying of Polycarbophil: An Indigestible, Particulate Substance.

ABSTRACT

The gastric emptying of indigestible meal components is currently thought to be dependent upon phase 3 motor activity. However, this concept is based on the gastric emptying behavior of large, noncompressible spheres which do not resemble food. We tested whether an indigestible substance could empty independently of phase 3 activity. Test meals consisted of polycarbophil (PC), an indigestible, particulate substance.

Dogs were fitted with gastric cannulas. Force transducers were implanted for chronic detection of antral and orad duodenal circular muscle activity. Meals of 30 and 90 gm radioactively-labeled PC were administered by oral-gastric tube. After 4 hours the stomach was drained and the percent PC that had emptied was calculated. Antroduodenal contractile activity was recorded during the 4 hour test time to determine if phase 3 activity aided in the emptying process. In addition, the contractile response to PC was compared with that seen after meals of canned dog food to assess whether PC represented a food-like stimulus.

The gastric emptying of large PC meals was not dependent on phase 3 contractile activity. Approximately half of the 90 gm meal emptied despite the absence of phase 3 throughout the 4 hour test time. The smaller PC meal (30 gm) delayed but did not prevent the recurrence of phase 3 activity. However, even after passage of phase 3, not all the smaller PC meal emptied, i.e., $\geq$ 13% remained in the stomach.

PC represented a food-like stimulus. PC, like food, delayed phase 3 reappearance and elicited fed state-like patterns of antroduodenal

contractions. The magnitude of the responses to polycarbophil and food were each independent of meal size.

We conclude that polycarbophil particles can empty from the stomach independently of phase 3 motor activity and that polycarbophil and canned food have similar antroduodenal motor effects. The gastric emptying of polycarbophil particles differs significantly from that reported elsewhere for large, indigestible spheres. The gastric emptying of indigestible meal components is not adequately modeled by a single test meal type.

INTRODUCTION

The stomach differentially empties liquids, digestible solids, and indigestible solids (1). Liquids empty rapidly, relative to digestible solids, which in turn empty faster than indigestible solids. After a mixed meal, the motility which characterizes the fasted state is converted to a typical fed-state pattern of contractions (2). As the meal empties from the stomach, the fasted-state motor pattern redevelops. In particular, a recurring episode of maximal contractile activity (phase 3, also called the burst) is reestablished (2,3). After a meal of digestible solids plus 7 mm diameter plastic spheres (representing indigestible solid), the fed-state motor pattern lasts until the digestible solid empties. The reappearing phase 3 contractile pattern then sweeps the spheres from the stomach (4). As a result, the gastric emptying of indigestible spheres has tacitly been looked to as a model for the gastric emptying of indigestible meal solids, especially for particles of greater than 2 mm diameter (1,4 review, see 5). Aside from this model, no further studies on the gastric emptying of indigestible meal residues have been performed.

Polycarbophil is a synthetic, hydrophilic, acrylate polymer that is currently employed as both an antidiarrheal and bulk-forming laxative (6). Upon hydration, its granules form discrete, insoluble gel particles of approximately 1-3 mm diameter (6). The gastric emptying of digestible solids, spheres, and probably polycarbophil each depends upon antroduodenal motor activity. In the case of indigestible spheres, the postprandial reappearance of antroduodenal phase 3 activity causes gas-

tric emptying (4). Whether the gastric emptying of, and the gastroduodenal motor responses to, spheres adequately represents all indigestible ingesta, and in particular polycarbophil, has not been investigated.

The present studies were designed to determine whether polycarbophil test meals required phase 3 activity to empty from the stomach. In addition the antroduodenal motor responses to polycarbophil were compared with those in response to canned food. Our results indicate that polycarbophil is a food-like stimulus and is not emptied from the stomach in the manner reported elsewhere for spheres.

METHODS

Surgical Model - Dogs were surgically prepared with gastric fistulas and antroduodenal recording units for the measurement of gastric emptying and attending circular muscle contractile activity, respectively. Three female dogs of mixed breed (10-15 kg) were each anesthetized with pentobarbital, 30 mg/kg, iv (Abbott Lab., Chicago, IL). Four strain-gage force transducers were surgically implanted in the transverse axis of the gastric antrum and duodenum. Units were situated 6 and 4 cm orad and 4 and 6 cm caudad to the gastroduodenal junction. The methods for gage fabrication and implantation have been published (7). In addition, a wide-bore cannula was implanted into the anterior aspect of the most dependent part of the stomach. The cannula was constructed of stainless steel tubing (2.0 cm i.d., 2.2 cm o.d.), had a barrel length of 5.2 cm, and had a flat, flanged base. The cannula was exteriorized through a stab wound made lateral to the midline incision creating a chronic gastric fistula. The dogs were allowed a 2-week recovery period prior to testing.

Test Meals - Five test meals were studied. The test meals consisted of polycarbophil, 30 and 90 gm (gift from A.H. Robins Co., Richmond, VA); canned dog food, 90 and 250 gm (Vets, Perk Foods Co., Inc., Terminal Island, CA); and a saline control. Polycarbophil meals were prepared by mixing 30 or 90 gm of the prehydrated, radioactively labeled gel in saline to yield 300 ml. The meal presented as gel particles plus free saline. The preparation of radioactively labeled polycarbophil gel (labeled with chromium-51, a gamma emmitter) has been re-

ported (8). The polycarbophil and saline meals, each measuring 300 ml, were administered orally using syringes and an oral-gastric tube. Canned food meals were administered in the usual manner.

Motility Studies - Dogs were fasted for 18 hours after which they routinely exhibited the typical interdigestive motility pattern (2,3). This pattern presents as a cycle comprised of 3 major phases. Phase 1, which lasts about 60 min, is the period of motor quiescence; during phase 2, which lasts about 30 min, contractions are more frequent and of variable amplitudes; phase 3, lasting 5-15 min, is marked by high amplitude contractions appearing at maximal frequency. These phases are also described as the basal, preburst and burst intervals, respectively (2). The complete cycle repeats on the stomach and small intestine approximately every 100 min. All meals were administered at the beginning of the phase of motor quiescence (phase 1, basal state).

In the fasted state, the phase 3 interval recurs approximately every 100 min. In preliminary studies, 90 gm polycarbophil meals delayed the reappearance of phase 3 for more than 4 hours. Because our primary interest was to examine whether the gastric emptying of polycarbophil could occur in the absence of phase 3 activity, 240 min, approximately the duration of 2 complete motility cycles, was chosen as the test time. This allowed both documentation of the dose-related delays of phase 3 activity and the determinaton of whether gastric emptying of the 90 gm meal could occur in the absence of phase 3 activity.

The antroduodenal contractile responses to meals containing polycarbophil were compared with those in response to canned dog food

and saline. Motor activity was assessed from 30 to 60 min after meal administration. This time interval was assessed because polycarbophil, food and saline meals each elicited motor patterns that became stable by 15-30 min after administration. Specifically, this sampling technique prevented confounding the responses with either the occasionally high amplitude contractions seen initially after saline meals or the variable response onset time after the solid meals. Once established, the contractile patterns appeared monotonous throughout the test time. Contractile responses were expressed as a percentage of the maximum contractile activity seen during the pretreatment phase 3 interval. Antral and duodenal motor responses were quantified similarly. First, the postprandial motor responses were indexed. The index was calculated as:

$$\text{weighted index} = \frac{1\ (\#\ \text{contractions } 20\text{-}49\%) + 2\ (\#\ \text{contractions} \geq 50\%)}{30\ \text{min}}$$

where response contractions were scored with one point if they measured 20-49% of the pretreatment phase 3 contractile amplitude and 2 points if they met or exceeded 50% of the pretreatment phase 3 amplitude. Dividing the numerator by the 30 min sample time yielded a per-minute index value.

In order to compare antral and duodenal contractile responses, the indexed values were then normalized by expressing them as a percent of the maximum possible per-minute index value which occurs during the pretreatment phase 3 interval. Antral and duodenal maximums were calculated according to the method for the weighted index. Idealized antral

and duodenal maxima were used throughout the analysis. On the average, antral and duodenal phase 3 contractions occur at a frequency of 4.5 and 18 cpm, respectively. Since phase 3 contractions are of maximal amplitude, each was scored with 2 points. Thus the maximum per-minute index values for the antrum and duodenum were calculated to be 9 and 36, respectively. The percent maximum response was used in all analyses and was calculated as:

$$\text{\% maximum response} = \left(\frac{\text{weighted index value}}{\text{maximum index value}}\right)100$$

Whether polycarbophil, like canned food meals, could delay post-treatment phase 3 activity was assessed. The times of reappearance of the post-treatment phase 3 intervals were measured after meals of saline, polycarbophil and canned food.

Gastric Emptying Studies - The gastric emptying of polycarbophil alone was studied. Meals were administered at the onset of the phase of antroduodenal motor quiescence (phase 1). Four hours after meal administration, the dogs were placed into slings. The gastric cannula was opened, and the stomach was allowed to drain by gravity. One L tap water was administered via the oral-gastric tube to rinse out the remaining gel. The entire effluent was then strained through gauze and dried (110°C x 18 h). Dried effluent was monitored for gamma radiation (Packard Auto Gamma Spectrometer, Downers Grove, IL). The total activity of the original test meal was calculated as (cpm/gm sample aliquot)(gm gel/meal). The amount of gel recovered from the stomach at 4

hours was expressed as a percent of the total original meal radioactivity and served (by subtraction) as an estimate of the amount of meal that had emptied. Each meal was tested twice in each dog.

Hydrated polycarbophil particles were observed to tenaciously stick to skin surfaces (personal observation). Whether a portion of the test meal could adhere to the gastric mucosa to confound estimates of gastric emptying was determined. Each dog was fed a 90 gm polycarbophil test meal; the gastric cannula remained closed. After 4 hours, gastric emptying was measured. The dogs were then killed with an overdose of pentobarbital, and the whole gut was excised. The stomach was resected and layed out along the greater curvature. The remaining polycarbophil was vigorously rinsed off and collected. The percent meal recovered in this manner was quantified. In addition, qualitative descriptions of the degree of gel adhesion to the gastric mucosa, the distribution of gel along the gut, and changes in the physical appearance of the gel particles were noted.

Data Analysis - The amounts of polycarbophil remaining in the stomach after meals of 30 and 90 gm were compared using a t test for paired values. Meal-related delays of the post-treatment phase 3 interval were assessed using Friedman's 2-way analysis of variance (ANOVA) (treatments vs. dogs) (9). This nonparametric test was used because all experiments were terminated at 240 min, which artifically fixed response values for the larger polycarbophil and meat meals. The antroduodenal motor responses to the various meals were compared using a 3-level fac-

torial design ANOVA. Treatments, gage locations, and dogs served as the factor levels (10).

RESULTS

Gastric Emptying - A significant percent of the 90-gram polycarbophil meal emptied during the 4 hour test period in the absence of phase 3 activity (vide infra). At 4 hours, the 30 gm meal had emptied more completely than the 90 gm meal (30 gm meal: 87 ± 7%, 90 gm meal: 73 ± 4%, n = 3 dogs, 1-3 obs./dog, $p < .05$). Similarly, the gastric emptying of the 90 gm meal, performed just prior to sacrifice measured 75 ± 5% (n= three dogs). However, these estimates of gastric emptying were probably significant overestimates. At autopsy, an additional 24 ± 7% of the 90 gm meal was recovered from the stomachs of the 3 dogs tested. Thus the percent meal emptied by 4 hours was actually closer to 51% (i.e., 75-24%) than the reported 75%. Nearly all of the gel particles remaining in the stomach had collected in the gastric antrum. The gel particles appeared unchanged, and no aggregates were noted. Further, the gel particles did not appear to be adhered to the mucosa even after 4 hours in the stomach.

At autopsy, gel was not recovered from the orad small intestine. However both dogs had accumulated significant amounts of the gel in the caudad small intestine. In one dog, the gel had migrated into the colon. In each dog, the gel maintained its original appearance while still in the stomach. In contrast, gel volumes appeared to increase appreciably in the small intestine and colon. Polycarbophil exhibits pH-dependent swelling (11,12). Gel volume changes of 10-fold are common after increasing the pH from 3 to approximately 7.

Motility Studies - Polycarbophil was a food-like stimulus. Both the polycarbophil and canned food meals delayed the reappearance of phase 3, relative to the saline control (Table 1). The 90 gm polycarbophil meal and the 250 gm canned food meal each delayed phase 3 activity for the entire 4 hour test period (Table 1). Taken with the gastric emptying studies, about 50% of the 90 gm polycarbophil meal had emptied despite the absence of phase 3 activity. The 30 gm polycarbophil meal delayed phase 3 activity less than the 90 gm meal. Although saline elicited antroduodenal contractions, it didn't delay the cyclic reappearance of the interdigestive phase 3 interval, relative to cycle reappearance time in the undisturbed fasted state (Table 1).

Both polycarbophil and canned food meals replaced the interdigestive quiescent motor phase with a typical, fed state motor pattern. Aside from the fed state pattern, polycarbophil did not elicit any distinctive pattern of gastric or duodenal contractions. Polycarbophil and canned food meals each elicited antral and duodenal responses which were consistently less than 20% of the maximum seen during the pretreatment phase 3 interval (Fig. 1). Test-meal-induced contractions were mainly of low or intermediate amplitude and frequency. Factorial analysis revealed that the antral contractile responses alone were not significantly increased after the various test meals, relative to saline. Duodenal responses also did not differ from control. However, duodenal contractile activity significantly exceeded antral activity after most meals (Fig. 1).

Table 1

Effect of test meals on time of reappearance of interdigestive phase 3 interval (min).[a]

			Test Meal				
			Polycarbophil (gm)		Food (gm)		p[b]
Dog	Fasted	Saline	30	90	90	250	
A	135[c]	145	177	>240[d]	>240	>240	
B	117	116	230	>240	>240	>240	
C	121	135	193	>240	196	>240	
$\bar{X}$±SEM	124±5	132±9	200±16	NA[e]	NA	NA	<.001

[a]Test meals given at the beginning of phase 1 of the interdigestive cycle

[b]Friedman (nonparametric) 2-way analysis of variance

[c]Each entry is the mean ± S.E.M. of 1-3 trials

[d]>240 = Test stopped at 240 min

[e]Not applicable

FIGURE 1.

Antral (hatched) and duodenal (open) contractile responses to test meals containing saline (S); canned food, 90 gm (F-90) and 250 gm (F-250); polycarbophil, 30 gm (P-30) and 90 gm (P-90). Vertical bars denote S.E.M. (n = 3 dogs, 1-3 observations per dog). Postprandial duodenal activity exceeded corresponding antral activities in most cases, $p < .05$ (*).

% Maximum Motor Activity per Minute
20
10
S
F-90
F-250
P-30
P-90
Test Meal
*
*
*

DISCUSSION

The present studies demonstrate that an indigestible meal substance can empty from the stomach without the aid of phase 3 contractile activity. This contrasts with the phase 3-dependent gastric emptying of large, noncompressible spheres which are thought to model indigestible meal residues (4). Our results are relevant to how indigestible substances such as dietary fibers might empty from the stomach. Fiber represents dietary components of plant origin that are not digested by the secretions of the gut (13). Upon mixture with water, fiber generally either forms a homogeneous gel or remains in particulate form. Recent studies show that homogeneous gel meals of guar gum or psyllium empty rapidly ($E^1/_2$ ca 10-40 min) and essentially independently of antroduodenal contractile activity (14). The gastric emptying of particulate fibers such as bran and alpha-cellulose alone have not been studied. However other workers have indirectly suggested that particulate fiber empties differently than plastic spheres. Mixtures of bran or alpha cellulose with digestible solids have each been shown to empty from the stomach slowly but steadily (15,16). The gastric emptying of polycarbophil and the reported emptying of fiber-meal mixtures suggests that the gastric emptying of all indigestible meal residues cannot be modeled by spheres.

Polycarbophil meals were incompletely emptied from the stomach at 4 hours. Despite the reappearance of post-treatment phase 3 activity, part of even the smaller polycarbophil meal remained in the stomach. Such slow emptying was not explained by adhesion of polycarbophil to the

gastric mucosa. However, aggregation could account for the slow emptying of these small gel particles. Polycarbophil particles are mechanically compliant. The simple act of squeezing a portion of the gel causes a partial loss of gel water, leaving a molded bolus (personal observation). The bolus readily rehydrates and loses its molded shape. In contrast to saline, polycarbophil does not exhibit any recognizable flow system. We propose that intragastric polycarbophil initially mixes like conventional digestible solids. Antral contractions, which force digesta into the terminal antrum, empty a small fraction of the meal and squeeze the balance of the polycarbophil, molding a large bolus. Because polycarbophil does not readily flow, it isn't retropelled effectively into the gastric body. Accumulation of the gel in the antrum was clear at sacrifice. However, remixture with gastric juice acts to rehydrate the bolus, allowing the particles to redisburse. The cycle repeats, and a partial emptying of gel particles occurs with every major antral contraction. Continual mixing and emptying is consistent with the fed state-like motor pattern induced by polycarbophil. The gastric emptying of polycarbophil is likely a slow, continuous process, similar to that of solid food.

The duration of the fed-state motor pattern was influenced by test meal size. The larger polycarbophil meal delayed phase 3 activity (which signals the end of the fed state) more than the smaller meal, presumably as a result of increased gastric distention and a longer gastric emptying time. Previous attempts to relate meal size to postprandial motor pattern duration have been confounded by concomitant in-

creases in meal caloric content (19,20). Polycarbophil is insoluble and indigestible and thus not a source of bioavailable calories. Results with polycarbophil suggest that the duration of the postprandial motor pattern can be markedly influenced solely by the size of a meal.

Large and small canned food meals elicited similar antroduodenal contractile responses. The constant duodenal responses of the present studies are consistent with the characteristically slow gastric emptying of digestible solid, where the duodenum is repeatedly presented with only small portions of chyme (18). Schang et al. (19) have demonstrated that even if the duodenum is directly perfused with solutions of increasing caloric concentration, the intestinal spike potential response (contractile correlate) is not enhanced. The motor responses to polycarbophil were also not meal size-dependent. Taken together this suggests that postprandial antroduodenal contractile activity is not a sensitive litmus of meal size or total caloric load. Thus polycarbophil represented a food-like stimulus for its effects on antroduodenal motility and phase 3 activity. In marked contrast to the effects of polycarbophil and food are those reported elsewhere for spheres. Spheres neither elicit fed state-like motility nor do they delay the reappearance of phase 3 activity (4).

The gastric emptying behavior and motor effects of polycarbophil clearly are not similar to those reported for spheres (4). Whether polycarbophil is a model for important indigestible particles such as dietary fibers is not established here. Indeed, a single modeling substance may not be adequate. The present studies, and those of others

(15), strongly suggest that particulate solids are not well represented by large spheres.

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CHAPTER 5

Effects of Laxative and Nonlaxative Hydrophilic Polymers on Canine Small Intestinal Motor Activity.

Abstract

A study was made of the effects of the bulk laxatives psyllium and polycarbophil (PC) and the nonlaxative pectin on canine jejunal motor activity. Pectin and psyllium meals presented as gels of concentration-dependent viscosity while PC meals presented as discrete gel particles. Measurements were made of the jejunal motility index and the time of reappearance of interdigestive phase 3 activity after each meal. Pectin and psyllium meals concentration-dependently increased jejunal motility and delayed the reappearance of phase 3 activity. Motor activity presented as randomly distributed contractions. In contrast, all PC meals elicited control level activity which presented as propagated clusters of contractions. Polycarbophil did not delay the reappearance of phase 3 activity. We conclude: a) bulk laxatives do not uniformly affect jejunal motility, and b) differences in polymer meal-induced motor effects are related to meal viscosities and probably the physical form of the meal.

Introduction

Laxatives are a chemically diverse group of compounds employed to alter stool frequency, volume and texture (1). Most laxatives are currently regarded as either intestinal secretogogues or bulk-formers. Secretogogues, e.g., castor oil, produce watery stools by promoting small intestinal secretion and propulsive small intestinal motor patterns (2,3, reviews see 1). Bulk-forming laxatives are all polymers; some are dietary fibers, others are synthetic. Bulk-formers such as psyllium (fiber) and polycarbophil (synthetic) increase stool volume and frequency (4,5). Bulk laxation is also associated with colonic motility changes. The addition of fiber laxatives such as bran or alpha cellulose to meals results in pronounced changes in the frequency (6) and organization (7) of proximal colonic, propagated spike potentials.

Most of the total gut transit time of bulk-forming laxatives is spent in the colon. Since stool formation occurs in the colon, bulk-laxation has been regarded as a colonic event. However, like secretogogue-laxation, bulk-laxation may have a small intestinal motor component. The addition of single doses of alpha cellulose or bran to meals replaces the typical, jejunal postprandial motor pattern with one of aborally-directed groups of contractions (8). If bulk-formers, like secretogogues, uniformly affect small intestinal motility, then psyllium and polycarbophil should also elicit

organized jejunal contractile activity. However, not all dietary fibers are laxatives. The fibers pectin and guar gum have no appreciable effect on stool volume or frequency (9,10). Whether laxative and nonlaxative fibers differentially and dose-dependently affect small intestinal motility has not been investigated.

Dietary fibers exhibit varying degrees of hydrophilicity (11) and fibers such as pectin and psyllium form homogeneous gels upon hydration. These gels exhibit concentration-dependent changes in flow properties such as viscosity (12,13). Increases in test meal viscosity have been associated with slowed rates of gastric emptying (13,14). Meal viscosity may also influence the intestinal motor response to test meals containing gel-forming fiber.

The present studies were performed to characterize the canine jejunal contractile responses to test meals containing increasing amounts of the laxative polymers psyllium and polycarbophil and the nonlaxative polymer pectin. In addition, the effect of polymer concentration on meal flow properties and the association between flow properties and intestinal motor activity were each examined.

METHODS AND MATERIALS

Surgical model - Four female dogs of mixed breed (10-15 kg) were each anesthetized with pentobarbital, 30 mg/kg, i.v. (Nembutal^{R}, Abbott Lab., Chicago, Il). Strain gage force transducers were surgically implanted into the transverse axis of the

orad jejunum using aseptic technique. The recording units were located 15, 30, 45, and 60 cm caudad to the Ligament of Treitz. The methods for gage fabrication and implantation have been reported (15). Dogs were allowed a two week recovery period prior to testing.

Test meals - Meals containing psyllium and pectin yielded homogeneous gels. In contrast, polycarbophil meals were non-homogeneous and thus were prepared differently. The fiber meals contained milled psyllium seed (dextrose-free) or citrus pectin (gifts from G. D. Searle & Co., Skokie, IL). Meals of 0.3, 1.0 and 3.0% w/v fiber were prepared by blending the fiber with 0.9% NaCl (saline) to reach a volume of 300 ml. A 5 second low speed pulse of blending (Oster) yielded homogeneous mixtures. This fiber concentration range bridged the fiber doses used clinically (on a weight basis) and also yielded meals of increasing viscosity (vide infra).

Polycarbophil test meals were prepared by stirring sodium polycarbophil granules (gift from A. G. Robins & Co., Richmond, VA) in saline to yield meals (0.3, 1.0 and 3.0% w/v) of 300 ml. Polycarbophil hydrated rapidly (within 1/2 hour) to yield gel particles of less than 3 mm diameter. In all cases, meal gel fractions never exceeded 150 ml.

Psyllium and pectin meals formed viscous suspensions within minutes after mixing. In contrast, hydrated polycarbophil par-

ticles rapidly settled in the meal saline; meals had to be stirred to disperse the gel particles. To facilitate feeding of the psyllium and pectin meals, they were mixed and immediately drawn into large bore syringes. Meals were then administered to the dogs via an oral-gastric tube. Polycarbophil was administered similarly after its initial hydration period.

Motility studies - Canine interdigestive motility patterns are well established (15,16). In the fasted state, three major activity phases - phases 1, 2 and 3 (initially termed the basal, preburst and burst states) occur in series. The entire series repeats approximately every 100 min. Phases 1, 2, and 3 are marked by contractions of low, intermediate and high frequency and amplitude, respectively. Since phase 3 is a brief interval (ca 10 min) of maximal amplitude contractions, it is often used to monitor the duration of the entire motility cycle (i.e., phase 3 to phase 3). Phase 3 is followed by phase 1. The effects of test meals and drugs on intestinal motor activity may be investigated during phase 1, which lasts about 60 min, without the contribution of spontaneous contractile activity to the muscle responses. In the present studies, all test meals were administered at the beginning of phase 1.

The effect of increasing meal polymer content on jejunal contractile activity was assessed for 30 minutes starting at the onset of the motor responses (usually immediately after adminis-

tration). Contractile responses were expressed as a percentage of the maximum contractile activty seen during the pretreatment phase 3 interval. ~~Antral and duodenal~~ jejunal motor responses were quantified similarly. First, the postprandial motor responses were indexed. The index was calculated as:

$$\text{weighted index} = \frac{1\ (\#\ \text{contractions } 20\text{-}49\%) + 2\ (\#\ \text{contractions} > 50\%)}{30\ \text{min}}$$

where response contractions were scored with a point if they measured 20-49% of the pretreatment phase 3 contractile amplitude, and two points if they met or exceeded 50% of the pretreatment phase 3 amplitude. Dividing the numerator by the 30-min sample time yielded a per-minute index value.

corrected 4/84 JR.

In order to compare ~~antral and duodenal~~ jejunal contractile responses, the indexed values were then normalized by expressing them as a percent of the maximum possible per-minute index value which occurs during the pretreatment phase 3 interval. ~~Antral and duodenal~~ maximums were calculated according to the method for the weighted index. Idealized ~~antral and duodenal~~ maxima were used throughout the analysis. On the average, ~~antral and duodenal~~ jejunal phase 3 contractions occur at a rate of ~~4.5 and 18~~ 17 cpm, respectively. Since phase 3 contractions are of maximal amplitude, each was scored with 2 points. Thus the maximum per-minute index values

for the ~~antrum and duodenum were~~ jejunum was calculated to be ~~9 and 36, respectively.~~ 37 The percent maximum response was used in all analyses and was calculated as:

$$\% \text{ maximum response} = \left(\frac{\text{weighted index value}}{\text{maximum index value}}\right) 100$$

Meals elicit typical fed state motility and delay the reappearance of phase 3 (15). In addition to indexed motor responses, the ability of polymer meals to delay the reappearance of interdigestive phase 3 activity was measured. Motility cycles were measured from the end of the pretreatment phase 3 interval to the beginning of the first postprandial phase 3 interval. In addition, the duration of the phase 3 interval was measured.

Motor responses to psyllium, pectin, and polycarbophil meals were each examined for differences in the patterns of contractions that they elicited. It became obvious that even the most viscous pectin and psyllium meals did not elicit organized motor patterns while all meals of polycarbophil did. Polycarbophil elicited jejunal contractions which appeared in discrete, aborally-directed groups. The ability of secretogogue laxatives to elicit such a contractile pattern, the "laxative-induced pattern" (LIP), has been reported (3). In this report, LIP will refer to these aborally directed groups of contractions in general and to one group of contractions in particular. The motor patterns in response to

increasing meal polycarbophil content were assessed for a) LIP frequency, b) the number of contractions per LIP and the amplitude of these contractions, relative to pretreatment phase 3 amplitude, and c) the effect of meal polycarbophil content on the aborad propagation rate of the LIP. LIP activity was assessed for 30 min after the organized motor pattern developed, which was usually about 15 min after meal administration.

Regional Distribution of Polycarbophil - After observing the effect of polycarbophil on jejunal activity, we hypothesized that polycarbophil elicited the LIP by collecting in the small bowel. Polycarbophil could represent a slowly progressing mass or series of intraluminal gel boluses. To test this hypothesis, four dogs were fasted and administered 90 gm meals of polycarbophil. Polycarbophil was radiolabeled with chromium-51, a gamma emitter. The methods for labeling and quantifying polycarbophil have been reported (17). After four hours, the dogs were sacrificed with anesthetic. Four hours was chosen because it represented the approximate half-empyting time of the meal from the stomach (18). The gut was then excised. The % test meal recovered from the stomach, the first and the second halves of the small bowel, and the colon were each calculated.

Data analysis - The effects of increasing meal polymer content on jejunal motor activity, motility cycle duration and post-treatment phase 3 durations were each assessed with a two-way

analysis of variance (dogs vs. meal concentration) (19). Polycarbophil-associated LIP parameters were assessed similarly. Differences in treatment means were identified with Duncan's multiple range test.

Fiber meal flow characteristics - The flow patterns of test meals containing increasing amounts of pectin and psyllium were each characterized using a rotational viscometer (Haake Rotovisco-12, MV1K bob and cup assembly). All measurements were made on samples maintained at 37°C. The viscometer was programmed to subject 40 ml meal samples to gradually increasing and then decreasing rates of shear (0→300→0 rpm) over an 8 min period. The shear stresses in response to shear rate were automatically plotted from which plots of viscosity vs. shear rate were constructed. Such a plot, the rheogram, relates meal viscosity to the rate of shear. Because the gels of dietary fibers can exhibit shear rate-dependent viscosities (13), comparisons of meal viscosities were made based on values obtained at the arbitrarily specified shear rate of 64 rpm. In addition, and of equal importance, the patterns of viscosity change with increases in shear rate, i.e., the flow pattern, were described for both psyllium and pectin meals.

In contrast to the homogeneous gels of psyllium and pectin, polycarbophil hydrated and formed gel particles. Polycarbophil meals behave like solids. Thus, the polycarbophil meal was not subject to viscosity determinations. The viscosity of the saline

control was measured using an Ostwald-Cannon-Fenske capillary viscometer.

RESULTS

Motility studies - Meals of pectin and psyllium each elicited jejunal contractile responses which averaged only 5-25% of the pretreatment phase 3 maximum response. Only the highest fiber concentrations tested elicited motor responses that exceeded those in response to saline (Fig. 1). Neither psyllium nor pectin elicited discernible patterns of jejunal motor activity at the concentrations tested (Fig. 2).

The motor responses to polycarbophil did not parallel those to pectin and psyllium. Polycarbophil did not significantly increase jejunal contractile activity at any dose tested, relative to saline (Fig. 1). In addition, the contractions seen with polycarbophil usually presented as an LIP (Fig 3). The onset time and frequency of LIPs were not dose-dependent (Table 1). Increases in meal polycarbophil content caused modest but significant increases in contraction amplitudes but did not change the number of contractions per LIP. Most LIP appeared to be propagated aborally over the 30 cm segment examined (Fig. 3). Propagation rate tended to be faster after smaller doses (Table 1). In many tests, one or more of the LIP would be absent from either the orad or caudad mechanogram suggesting local genesis of the contractions without propagation over the segment monitored.

FIGURE 1.

Effect of increasing test meal psyllium, pectin, and polycarbophil content on jejunal contractile activity, relative to saline control (o). Responses indexed as % of the pretreatment phase 3 maximum. Values represent $\bar{x} \pm$ SEM; n = 4 dogs for psyllium and polycarbophil meals, 3 dogs for pectin meals; 1-6 trails/dog. Differences among treatment means detected with a two-way analysis of variance (treatment vs dogs). Differences significant at $p \leq .05$.

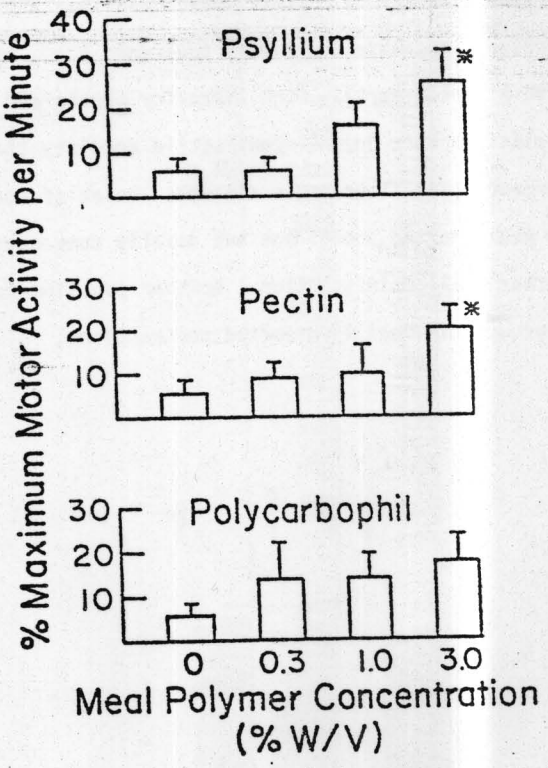

% Maximum Motor Activity per Minute
Psyllium
40
30
20
10
*
Pectin
30
20
10
*
Polycarbophil
30
20
10
0
0.3
1.0
3.0
Meal Polymer Concentration
(% W/V)

FIGURE 2.

Effect of high fiber content test meals on jejunal contractile activity, relative to saline control. Each meal was administered after interdigestive phase 3 activity sudsided, i.e., at the beginning of phase 1 (hatch mark). High viscosity pectin and psyllium meals each elicited more jejunal contractile activity than saline; lower concentration fiber meals did not. Onset of contractile response to meals varied among dogs but usually commenced within minutes after meal administration. Neither psyllium nor pectin elicited groups of aborally-directed contractions.

SALINE
PSYLLIUM
PECTIN
1min

TABLE 1

Effect of Increasing Meal Polycarbophil Content on Selected Motility Parameters

Parameter	(n)[a]	Meal Polymer Concentration (% w/v) 0	0.3	1.0	3.0	p[b]
LIP onset (min)	4	NOT present	24 ± 13[c]	38 ± 14	30 ± 10	>.05
LIP per 30 min	4	NOT present	7 ± 4	9 ± 1	9 ± 2	>.05
LIP amplitude (% max)	4	NOT present	38 ± 6	55 ± 3	59 ± 4	<.05
# contractions/LIP	4	NOT present	11 ± 2	12 ± 0	10 ± 1	>.05
LIP propagation rate (cm/min)	3	NOT present	21.2 ± 5.9	8.3 ± 0.7	11.1 ± 2.3	>.05
Motility Cycle duration (min)	4	92 ± 11	130 ± 20	152 ± 16	149 ± 24	>.05
Phase 3 duration (min)	4	6 ± 1	5 ± 0.5	5 ± 0.3	5 ± 0.6	>.05

a) Number of dogs (1-6 obs. per dog).
b) Two-way analysis of variance. Means NOT underlined by a common line are different, $p < .05$
c) Mean ± S.E.M.

FIGURE 3.

Jejunal motor response to a polycarbophil test meal. Each concentration of polycarbophil elicited a similar pattern. Clusters of contractions appear propagated over three equidistant recording sites totalling 45 cm of mid jejunum. Most clusters appear at each site but a significant number appeared spontaneously at caudad sites (i.e., B vs A); others were extinguished before traveling the 45 cm distance.

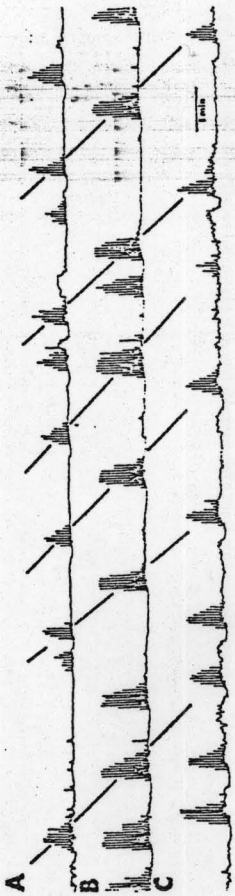

A
B
C
1min

TABLE 2

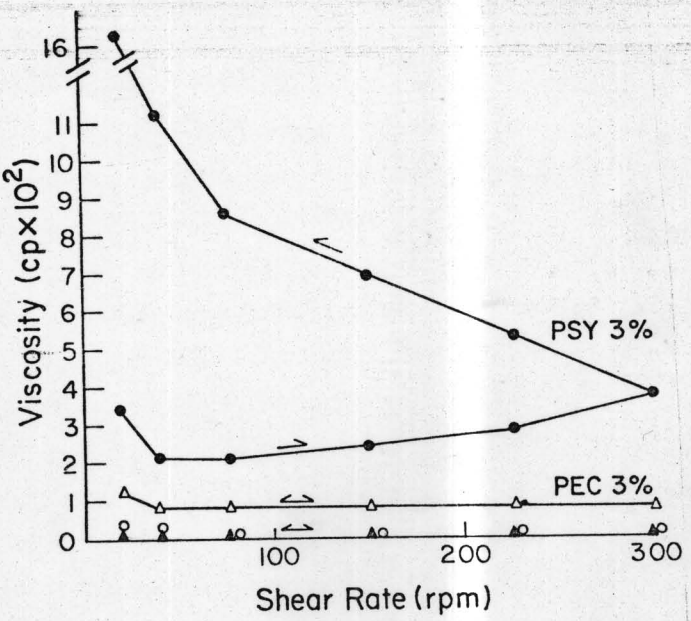
Effect Of Increasing Meal Pectin Or Psyllium Content
On Selected Motility Parameters

Parameter	Fiber	(n)[a]	Meal Polymer Concentration (% w/v) 0	0.3	1.0	3.0	p[b]
Motility cycle duration (min)	psyllium	3	94 ± 15	101 ± 21	130 ± 17	176 ± 3	<.05
	pectin	2	79	66	94	117	n.a.[c]
Phase 3 duration	psyllium	3	5 ± 1.3	5 ± 0.6	5 ± 0	5 ± 0.3	>.05
	pectin	2	6	5	8	6	n.a.

a) number of dogs, 1-6 obs. per dog.
b) Two-way analysis of variance, Means not underlined by a common line are different by Duncan's multiple range test.
c) No analysis performed. Experiments performed in two dogs only.

FIGURE 4.

Flow diagrams for psyllium and pectin test meals. Arrows indicate shear:viscosity relation as shear rate increases and then decreases. One percent meals were less viscous than the 3% meals over the range of shear rates tested. Psyllium (1%) and both pectin meals exhibited pseudoplastic flow where increases in shear rate resulted in an initial decrease followed by relatively minor changes in viscosity. In contrast, psyllium (3%) exhibited dilatant flow. Both increases and decreases in shear rate resulted in dramatic increases in viscosity. The separation of up and down curves revealed thixotropy. Curves for saline and 0.3% pectin and psyllium meals were essentially superimposable on those for the 1% fiber meals.


Viscosity (cp x 10²)
16
11
10
9
8
7
6
5
4
3
2
1
0
100
200
300
Shear Rate (rpm)
PSY 3%
PEC 3%

Among the three concentrations of psyllium tested, only the 3.0% meal delayed the reappearance of the post-treatment phase 3 interval (Table 2). In two dogs, pectin tended to lengthen the motility cycle duration. In contrast, even high doses of polycarbophil did not significantly delay the reappearance of the posttreatment phase 3 interval (Table 1). None of the meals affected the brief duration of phase 3 (Tables 1,2).

The ability of pectin and psyllium meals to delay phase 3 activity probably did not last more than 1-2 cycles. Each dog exhibited its own characteristic interdigestive motility pattern periodicity (time from phase 3-to-phase 3) prior to the next day's test and throughout the 1-2 month test period. Thus, treatments had no lasting effect on interdigestive motor patterns.

Regional distribution of polycarbophil - In tests followed by sacrifice at 4 h, 13 ± 5% of the 90 gm polycarbophil meal was recovered from the caudad half of the small intestine which probably accounted for the motor patterns seen. Polycarbophil appeared either as a column or boluses in series along the ileum. Most of the meal remained in the stomach (53 ± 3%) while 16 ± 2% had reached the colon. Essentially none of the meal (3 ± 2%) was recovered from the duodenum and orad jejunum. The usual recovery of 90 ± 3% (range 85-97%, 5 ± 2% spillage) of the meal confirmed the stability of the gel-isotope bond *in vivo*. Full recovery of the label plus the unaltered appearance of the gel in the colon

suggested that polycarbophil was not degraded in the gut. It was noted that although the particulate gel appearance was maintained, the volume of gel recovered from the small bowel and colon greatly exceeded that volume originally administered. This reflected the tendency for polycarbophil to swell more in neutral or alkaline media than in acidic media (20).

Test meal viscosities - Psyllium and pectin test meal viscosities were each concentration-dependent. The 3.0% psyllium and pectin meals were each more viscous than their corresponding 1.0 and 0.3% meals throughout the range of shear rates tested (Fig. 4). Both 1.0 and 0.3% psyllium and pectin meals were watery and considered similar in viscosity to the saline control (0.95 cp, not shown).

At the highest concentrations tested, 3.0% psyllium and pectin meals exhibited different flow patterns in response to increasing shear rate (Fig. 4). Psyllium exhibited dilatant flow, depicted by a nonlinear increase in viscosity as shear rate increased. As the shear rate decreased (return curve), viscosity increased. This flow pattern is described as shear-thickening; after enough time without agitation or shear stress, the psyllium 3.0% gel would return to its original viscosity (343 cp). In contrast, pectin exhibited pseudoplastic flow, depicted by a shear rate-dependent decrease in viscosity followed by a Newtonian-like stabilization of viscosity (Fig. 4). Thixotropy was not evident.

Despite differences in flow patterns, the 3.0% psyllium meal was more viscous than the 3.0% pectin meal throughout the range of shear rates studied. For example, the 3.0% psyllium meal was 2.5-, 2.8-, and 4.6-fold more viscous than the 3.0% pectin meal at shear rates of 75, 150, and 300 rpm, respectively (Figure 4).

DISCUSSION

As a group, bulk-forming laxatives are not distinguished by their effects on small intestinal motility. Psyllium elicited randomly occurring contractions while polycarbophil elicited a distinct pattern of contractions. This difference contrasts with the propagated jejunal contractions which are uniformly produced by chemically dissimilar secretogogues such as castor oil and magnesium sulfate (1,3). However, bulk laxation is invariably associated with increases in stool weight. Since bran, alpha cellulose, psyllium and polycarbophil each increase stool weight, they may all elicit similar colonic motor effects (1,4-7). Bran and alpha cellulose modify the appearance of propagated colonic myoelectric patterns in pigs (6) and dogs (7), respectively. Whether different bulk laxatives elicit qualitatively similar colonic motor patterns within a species has not been studied.

The present studies suggest that the physical form of intraluminal content can influence intestinal contractile patterns. Polycarbophil formed discrete gel particles and elicited aborally-directed groups of contractions. In contrast, meals of psyllium

and pectin presented as homogeneous gels which elicited randomly appearing contractions. This same dichotomy has previously been reported. The fibers bran and alpha cellulose both retain their particulate appearance after hydration, and both generate aborally-directed groups of jejunal contractions (8). In contrast, even exceedingly viscous meals of guar gum (relative to the present 3.0% pectin meals) do not elicit organized motor activity (8). Solid particles probably do not flow in the intestine as readily as fluids. Polycarbophil accumulated in and distended the caudad jejunum which may have caused laxative-induced pattern (LIP). Simple luminal distention with water causes an aborally-directed motility pattern in rabbit ileum (22). However, the LIP was detected significantly orad (ca 12-24 inches) to the distended jejunal region. Thus, the motor pattern was probably initiated both locally by polycarbophil in transit and reflexly by distention of the caudad jejunum.

The highest concentration psyllium meal delayed the reappearance of post-treatment phase 3 activity by about one hour, relative to the interdigestive control. Lower concentration fiber meals had no delaying effect. This delay probably reflected the relatively slower gastric emptying of the high concentration fiber meals. In other studies, 1.0% and 3.0% psyllium meals exhibited half-emptying times of 13 and 40 minutes, respectively (13).

Pectin-related delays of phase 3 were also probably due to slow gastric emptying.

Polycarbophil elicited aborally directed groups of jejunal contractions (the LIP). In other studies from this laboratory, polycarbophil did not elicit the LIP on the duodenum (18). This difference is consistent with the accumulation of polymer in the caudad but not orad small intestine. The lack of duodenal accumulation was likely the result of small amounts of gel being propulsed through the orad duodenum, typical of the postprandial delivery of chyme. The duodenum does not engage in net fluid absorption, relative to the jejunum and caudad bowel (23). Small amounts of polycarbophil gel particles may have been delivered to the jejunum in the duodenal fluid stream. Accumulation of the gel would then be expected to begin in the caudad jejunum upon absorption of the accompanying fluid. The differential accumulation of gel only in the caudad bowel and the absence of any attending intraluminal water supports this explanation.

Polycarbophil meals selectively interrupt interdigestive motility cycles at the gastroduodenal but not the jejunal level. In contrast to the present studies of jejunal motility, identical polycarbophil meals were reported to delay the post-treatment reappearance of gastric and duodenal phase 3 activity (18). Such selective disruption of the interdigestive cycles at different levels of the gut has been reported previously. Distention of the

stomach with a balloon delays gastroduodenal but not mid-to caudad jejunal phase 3 activity (16). Both balloons and polycarbophil distend the stomach to simulate a fed state and interrupt the interdigestive cycle. In the present studies, examination of the gastrointestinal tract four hours after meal ingestion revealed that essentially no polycarbophil was found in the duodenum or orad jejunum. Both the balloon effect and the present autopsy findings suggest that the absence of intraluminal content allowed the reappearance of phase 3 in the orad jejunum.

The present studies highlight the difficulties associated with relating fiber gel viscosity to intestinal motor activity. Both pectin and psyllium meals exhibited concentration-dependent increases in viscosity over the entire range of shear rates tested. Thus, for both psyllium and pectin meals, increases in jejunal motor activity were positively associated with increases in viscosity. However, jejunal motility apparently is not a sensitive indicator of meal viscosity. A threshold effect may account for the similar, control-level motor responses to meals of 0.3 and 1.0% fiber. In addition, a lack of sensitivity is demonstrated by the similar motor responses to 3.0% psyllium and pectin meals despite viscosity differences of 2- to 5-fold over the shear rates tested. Ideally, a relation between motility and viscosity would be based on the motor activity associated with a meal of a particular viscosity value. However, a strict relation cannot be

derived for fiber gels which exhibit nonNewtonian flow. The shear forces, i.e., the jejunal contractions, acting to move the gel in the bowel were continually changing; therefore, the gel viscosity was changing too. Thus, for nonNewtonian meals, the viscosity: motor activity relation cannot be known. It follows then that comparisons of the motility:viscosity relation between non-Newtonian meals of different concentrations or which exhibit different flow patterns also cannot be made (e.g. psyllium 3.0% vs psyllium 1.0%; psyllium 3.0% vs pectin 3.0%). Studies relating meal viscosity to gut motor function will require Newtonian liquids. Such substances retain characteristic viscosity irrespective of the shear forces (contractions) applied.

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The present studies were motivated by the recent observation that hydrophilic polymers attenuate post-prandial glycemia probably in part by slowing the gastric emptying of meal carbohydrates. Examination of post-prandial gastroduodenal motor responses and test meal emptying patterns represented a unified approach toward the characterization of polymer meal emptying. In addition, the availability of hydrophilic polymers that formed homogeneous gels upon hydration (psyllium, pectin and guar) and a polymer that retained its particulate form after hydration (polycarbophil) allowed for the examination of the gastric emptying of and the gut motor responses to distinctly different physical forms of polymers.

Markers were developed to permit measurement of the gastric emptying of viscous and particulate meals of hydrophilic polymers. Insoluble sephadex cation exchange resin was radiolabeled with $^{51}CrCl_2$ and suspended in sufficiently viscous meals of guar and psyllium. Polycarbophil granules were hydrated with saline, in which $Na_2{}^{51}CrO_4$ had been dissolved, to yield the radioactive gel particles. Meal half-emptying times were more conservatively estimated when based on isotope recovery than when based on solids alone. The utility of the meal labels was highlighted with the polycarbophil meals which emptied slowly and were extensively diluted by non-meal solids.

The gastric emptying of psyllium and guar meals was concentration-dependently slowed. This slowing was directly associated with increases in meal viscosity; postprandial antroduodenal motility did

not influence emptying. The present studies focused on how guar and psyllium affected the gastric emptying of an idealized meal. The effects of polymers on the gastric emptying of conventional solid-liquid meals will be more complex. For example, the addition of guar gum to a mixed meal does not alter the emptying time of the meal liquids, but slows the emptying of the meal solids (Chapter 1, ref. 146). This is the direct result of mixing the polymer with the solid phase of the meal but not the liquid phase. Whether a polymer affects test meal viscosity and emptying will depend on the amount and type of polymer used, the volume of meal liquids, the amount of meal solids, the meal phase with which the polymer is mixed and the thoroughness of mixing during meal preparation and in vivo.

Meals of polycarbophil particles elicited fed statelike antroduodenal motility. Half of a 90 gm meal emptied from the stomach in 4 hours, independently of phase 3 motor activity. The gastric emptying of and the motor responses to polycarbophil may model those for particulate dietary fibers such as bran and vegetable matter. Further studies will be needed to establish this. However, the present studies and studies of meat-fiber mixtures both document that the gastric emptying of small, indigestible particles is not modeled as was previously thought, i.e., by large spheres. Whether the gastric emptying of indigestible meal residues can or should be modeled by one substance is uncertain.

The jejunal motor responses to laxative and nonlaxative hydrophilic polymers seem related to polymer form and not laxative properties. Homogeneous gels of the laxative psyllium and the nonlaxative

pectin caused modest, concentration-dependent increases in jejunal motility. The motor effects were positively associated with increases in meal viscosity. In contrast, particulate gel meals of polycarbophil did not stimulate jejunal motility but reorganized control-level activity. Similar results reported elsewhere support the possibility that solid particles and viscous fluids elicit different intestinal motor effects. Whether these observations are important to small intestinal transit and absorption remains to be studied.

APPENDIX A

GASTRIC EMPTYING OF HOMOGENEOUS GEL TEST MEALS IN DOGS WITH GASTRODUODENAL CANNULAS.

Introduction

We wondered whether the orad duodenum regulated the gastric emptying of viscous test meals. Comparison of gastric emptying when the meal was diverted from the duodenum with that when the meal interacted with the duodenum would provide such information. Duodenal motility helps to regulate the gastric emptying of other test meals (e.g., liquids containing fatty acids). In the present case a requirement for the duodenum might be reflected by a high level duodenal contractile response when the meal contacted the duodenum. In the event that emptying was hastened by meal diversion, a reduction of attending duodenal contractile activity would suggest a duodenal role in the control of emptying of viscous ingesta.

This approach was abandoned when it became clear that control motility patterns were disrupted by the presence of the cannula at the gastroduodenal junction. Thus motor responses to test meals could not be evaluated. The gastric emptying results are presented and discussed with reference to results obtained in dogs having mid-duodenal cannulas (Chapter 2).

Method

Two dogs were surgically fitted with T shaped cannulas situated at the gastroduodenal junction. This placement allowed for complete

diversion of the gastric effluent from the duodenum. Strain gage force transducers were implanted on the terminal antrum and orad duodenum. Duodenal units were located 4 to 6 cm caudad to the cannula base. Details of the experimental model are given in Chapter 2. After recovery, the dogs were subjected to tests of gastric emptying. The gastric emptying of and the antroduodenal motor responses to 3 test meals (saline, psyllium 3% and guar gum 1.5%) were studied.

Results

Control motility - Duodenal interdigestive motility cycles were absent in nearly all experiments (n = 20). When present, cycles were prolonged (140-180 min), relative to historical controls (100 min, see Chap. 2). Interdigestive duodenal motor patterns were replaced with groups of maximal amplitude contractions. These groups were propagated aborally and were similar to those jejunal contractions described in response to meals of polycarbophil (Chapter 4). Antral interdigestive activity was replaced with continuous contractions of intermediate or high amplitude.

Gastric emptying - Test meals of saline, guar gum (1.5%) and psyllium (3%) emptied with half-emptying times of 9, 23, and 21 min, respectively (n = 2 dogs, 2-3 obs./dog). The fiber meals emptied faster when the gastric effluent was diverted from the duodenum than when it was collected from the mid-duodenum (compare with guar 1.5%: $E^1/_2$ = 34 min; psyllium 3%: $E^1/_2$ = 40 min, Chapter 2).

Motor responses to meals - Fiber meals elicited varying degrees of duodenal motor activity despite being diverted from the duodenum. Contractions frequently presented in a phase 3-like pattern, or a fed state-like pattern. Occasionally there would be no noticeable duodenal response. Antral activity was fed state-like. Antral contractions were continuous but of intermediate or maximal amplitude.

Discussion

Interdigestive motor activity - Replacement of interdigestive motility cycles with aborally-directed groups of contractions suggests that the duodenum may have been acting to move the cannula from the gastroduodenal area. This pattern can occur both orad and caudad to a distending stimulus. The recording units were situated about 5 cm caudad to the cannula. Thus the aborally-directed contractions were sustained 5 cm caudad to the distending stimulus. In other studies, polycarbophil meals caused distention of the caudad intestine (Chapter 4). Aborally-directed contractions were detected 50-75 cm orad to the distending stimulus. The patterns are probably reflex in origin and protective in nature.

Interdigestive motility cycles were abolished by distention of the gastroduodenal junction with a cannula. In contrast, in other studies, placement of a cannula at the mid-duodenum did not disrupt interdigestive cycles. The reason for the differences of effect is not clear. Mid-duodenal cannulation required no special surgical approach; no tension was placed on the bowel. However, placement of a cannula at the gastroduodenal junction required mobilizing the

gastroduodenal area by cutting the hepatoduodenal ligament. Once freed, the bowel segment was attached to the peritoneal wall for cannulation. The tension placed on the bowel segment plus division of any nerves within the ligament probably caused the disruption of interdigestive motor patterns.

Gastric emptying - High viscosity guar and psyllium test meals emptied rapidly in dogs with gastroduodenal junction cannulas, relative to dogs with mid-duodenal cannulas (Chapter 2). This hastened emptying probably reflects the much more vigorous antral response to meals than was seen in dogs with mid-duodenal cannulas (Chapter 2).

Duodenal contractile responses to fiber meals were highly variable both within and between dogs. This contrasts with the almost total lack of duodenal motor activity in response to the same fiber meals in dogs with mid-duodenal cannulas (Chapter 2). A combination of the presence of the gastroduodenal cannula plus gastric distention probably accounts for the unexpected postprandial duodenal activity.

APPENDIX B

EFFECTS OF GUAR GUM ON JEJUNAL MOTOR ACTIVITY.

Guar gum is a hydrophilic polymer without appreciable bulk laxative effects (vide supra, pp. 71-72). Upon hydration, guar forms a homogeneous gel. In Chapter 4, the jejunal motor effects of test meals containing laxative and non-laxative hydrophilic polymers were reported. The effects of guar were also examined as part of that study. Results were obtained in one dog.

Guar test meals elicited jejunal motor responses which were indistinguishable from those in response to pectin and psyllium meals. The more viscous guar meal (1.5% w/v) appeared to elicit more contractions per time than the less viscous meals (0.3, 1.0%). Contractions were of intermediate frequency and amplitude, relative to pretreatment phase 3 activity. No organized patterns of contractions were evident. Guar, like pectin, exhibits pseudoplastic flow (Chapter 2). The significance of the results with guar is discussed in Chapter 4.

APPENDIX C

Examination of the Viscosity of Duodenal Effluent After Meals of Dietary Fiber.

(Supplement to Chapters 2 and 3.)

INTRODUCTION

The method of labeling viscous fiber suspensions with ^{51}Cr-CM-Sephadex for the purpose of measuring gastric emptying has been described (vide supra, Chapter 2). In that report, indirect evidence was offered to argue that this marker remained adequately suspended in the meal for the period of 50% of test meal gastric emptying. The present data are direct evidence that psyllium (3%) and guar (1.5%) suspensions remain sufficiently viscous in vivo to suspend the ^{51}Cr-CM-Sephadex marker during the period of gastric emptying.

METHOD

The details of the experimental model, the test meals and the test protocols are given in Chapter 2. Briefly, in 2 dogs of that study, the viscosity:shear rate relations were examined for samples of duodenal effluent recovered after meals of guar gum (1.5%) and psyllium (3%). Effluent samples were taken from the 15-to-30 min post-feeding collection interval. Thus these samples represented effluent emptying from the duodenum during the completion of the test meal half-emptying time. Each meal was tested once in each dog. Viscosities were

assessed according to the methods outlined in Chapter 3 (NB: An SV-1 bob and cup assembly was used for the present observations. This contrasts with the MV-1 assembly used in the studies of Chapters 3 and 5. As a result, the shear rates employed range from 0 → 114 → 0 instead of 0 → 300 → 0 rpm). The viscosities of the duodenal effluents were compared to the viscosities of test suspensions known to be at minimum fiber content for the suspension of the meal marker (i.e., psyllium 2% and guar 1%).

RESULTS

Duodenal effluents collected after meals of psyllium (3%) and guar (1.5%) exhibited greater viscosities than the control suspensions (psyllium 2% and guar 1%) over the range of shear rates tested (figures 1 and 2). The psyllium flow curves revealed a loss of dilatancy, perhaps because of the addition of secretions to the suspension in vivo.

DISCUSSION

These data, albeit limited in number, document that the fiber meals of highest concentration, used in the studies of Chapters 2 and 3, retain sufficient viscosity to suspend the meal marker ^{51}Cr-CM-Sephadex over the course of the gastric emptying of at least 50% of the test meals.

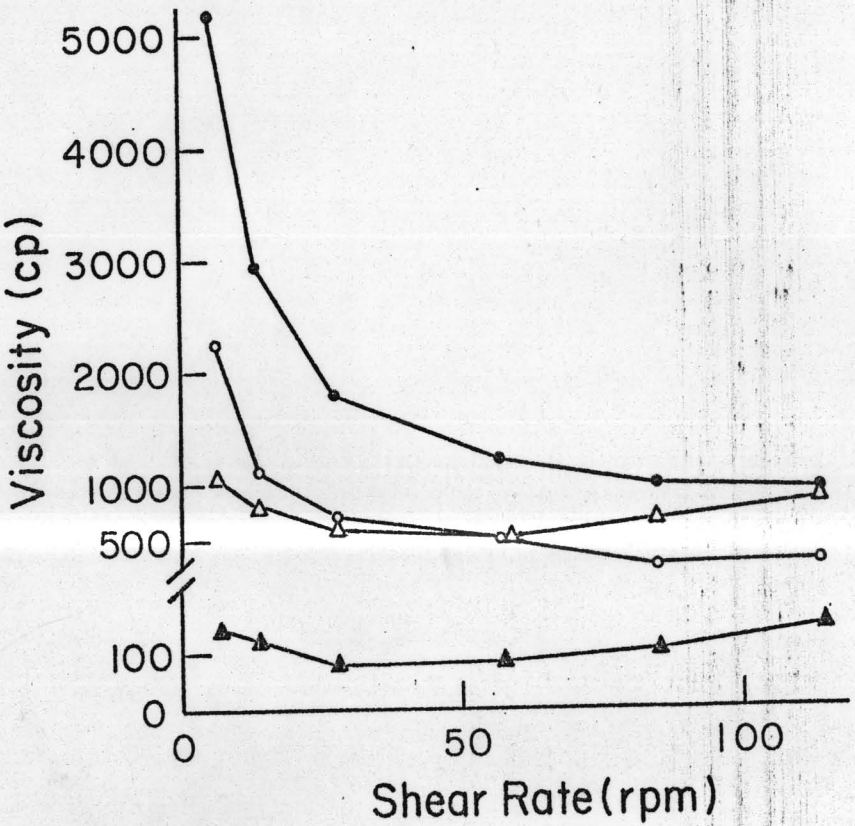
FIGURE 1.

Shear rate:viscosity relation for duodenal effluent collected after meals of guar gum 1.5%. Viscosity values for effluent collected from dog A (open circles) and dog B (open triangles) are not different from those values for the control guar 1.5% suspension (closed circles). Note that the viscosity values for guar 1.0% (closed triangles) are well below all other values. Since guar 1.0% is the minimum fiber concentration for the suspension of the meal marker (^{51}Cr-CM-Sephadex), this data shows that the effluent from guar 1.5% meals retains the viscosity necessary to suspend the meal marker *in vivo*.

Viscosity (cp×10³)
10
8
6
4
2
0
0
50
100
Shear Rate (rpm)

FIGURE 2.

Shear rate:viscosity relation for duodenal effluent collected after meals of psyllium 3.0%. Viscosity values for effluent collected from dog A (closed circles) and dog B (open circles) are not much different from those values for the control psyllium 3% (open triangles) suspension. Note that the values for psyllium 2% (closed triangles) are well below all other values. Since psyllium 2% is the minimum psyllium concentration for suspension of the ^{51}Cr-CM-Sephadex meal marker, this data shows that the effluent from psyllium 3% meals retains the viscosity necessary to suspend the meal marker *in vivo*.


5000
4000
3000
2000
1000
500
100
0
Viscosity (cp)
0
50
100
Shear Rate (rpm)

APPENDIX D.

MIGRATION OF SOLUBLE ^{51}Cr FROM A GEL PHASE TO AN ADJACENT WATER PHASE

INTRODUCTION

A valid test meal marker must remain with the meal under all conditions. Homogeneous gel meals of psyllium and guar were found to be uniformly labeled with water-soluble $^{51}CrCl_2$ *in vitro*. However, gastric emptying studies showed that gut secretions were incorporated with the meal during the emptying process. This raised the possibility that the isotope marker might migrate from the test meal gel phase to secretions, down a concentration gradient. Such an effect could cause underestimates of gastric emptying time, particularly if secretions emptied before the gel. Thus a test was performed to determine whether soluble $^{51}CrCl_2$ could migrate from a gel phase to an adjacent aqueous phase.

METHOD

Meals of psyllium (3o/o) and guar (1.5o/o) were each prepared as described in chapter 2. $^{51}CrCl_2$ was dissolved in the meal saline prior to mixing. The gel was placed in a 1L beaker and allowed to set. Once the gel was firm ca 30 min , 100 ml saline was layered onto the gel phase. Two ml samples of the saline phase were taken at 0, 15, 30, 45 and 60 min. The percent meal radioactivity that had migrated into the saline phase was calculated as:

$$\left[\frac{(\text{cpm/2 ml aliquot x ml saline layer})}{(\text{original meal cpm})}\right] 100$$

This same experiment was performed using the sephadex-bound Cr-51 to show that immobilizing the isotope prevented migration.

RESULT

Approximately 5 percent of the psyllium meal and 9 percent of the guar meal isotope migrated to the saline phase over the 60 min test time. The resin-bound marker did not migrate (table 1)

COMMENT

The experimental conditions of this test were conservative; more of the gel mass would be interfaced with secretions in vivo and isotope migration could be enhanced. Since the resin-bound marker did not migrate, it is the preferred marker for studies of gel meal gastric emptying.

Table 1.

Soluble Cr-51, but not resin-bound Cr-51, migrates from a meal gel phase to an adjacent saline phase.

Marker form	Meal	Cumulative percent cpm in saline at 60 min.
soluble	psyllium	5
	guar	9
resin-bound	psyllium	0
	guar	0

Evidence That Polycarbophil Can Act As A Physical Support for Aqueous Solutions for the Purposes of Sustained Release of Drugs.

I) Inability of $^{51}CrCl_2$ to Bind to Polycarbophil.

INTRODUCTION

A water-soluble gamma-emitter was sought as a label for polycarbophil particles. Both $^{51}CrCl_2$ and $Na_2{}^{51}CrO_4$ were tested. The results for chromate are reported in Chapter 2. The results obtained for $^{51}CrCl_2$ are reported here.

METHOD

$^{51}CrCl_2$ was dissolved in saline. This solution was used to hydrate polycarbophil granules (details of procedure see Chapter 2). After hydration, 4 successive rinses of the labeled gel with pH 3 saline were performed. The percent radioactivity per gram gel was determined after each rinse. Six samples were taken after each rinse.

RESULT AND COMMENT

Radioactivity per gram gel decreased by about 20 percent with each successive rinse (mean percent remaining after each rinse: 75, 59, 41, 22). In contrast, $Na_2{}^{51}CrO_4$ was not washed away as rapidly from the gel under similar experimental conditions (Chapter 2).

$^{51}CrCl_2$ was judged to be an unsuitable isotopic form of Cr-51 for the purposes of labeling polycarbophil particles. In a related sense, the leaching of $^{51}CrCl_2$ suggests that certain drug molecules could behave similarly. PC could therefore act as a physical support for the sustained release of drugs.

APPENDIX E

II) Hydration of Polycarbophil Granules with Atropine Solution to Achieve Sustained Mydriasis in the Rat.

INTRODUCTION

The slow leaching of ^{51}Cr (as $^{51}CrCl_2$) from polycarbophil (PC) gel particles suggested that a water-soluble drug could also be released slowly from the gel to provide a sustained biological effect. The present experiments were done to determine whether hydration of PC granules with a solution of atropine sulfate could produce a sustained mydriasis in the rat.

METHODS

Animal model - Male Sprague-Dawley rats (135-150 gm) were housed individually and deprived of food and water during the experiment. Rats were anesthetized with ether and underwent celiotomy. The duodenum was identified and a 5-7 mm incision was made along the antimesenteric border using iris scissors. A #5 gelatin capsule containing the treatment was inserted into the duodenum and pushed caudad to the incision site. The incision was then closed with 3-0 silk using a continuous suture technique. The midline incision was closed similarly.

Dosage form - All treatment doses were encapsulated (#5, gelatin) and administered intraduodenally. Intraduodenal administration was used to favor a more rapid onset of effect, relative to that after intragastric administration. Atropine sulfate (Sigma, St. Louis, MO; 5 mg/Kg) was dissolved in 0.9% NaCl (saline) to provide the dose required in about 0.1 ml. Rats received either atropine alone, atropine plus 25 mg PC granules (gift from A. G. Robins & Co., Richmond, VA), or 25 mg PC granules plus 0.1 ml saline as the control. For one group of rats, mixture of the encapsulated PC granules with the 0.1 ml saline or atropine was performed immediately prior to implantation of the capsule. Another group of rats received a PC-atropine mixture which had previously been mixed and then dried (room temperature x 24 H) in the capsule.

Test paradigm - Rats received treatments at time-0. Pupil diameter was estimated at 0.5, 1, 2, 4, 6, 8, 10, 12 and 14 hours after dosing. Pupil diameters were scored as follows: pinpoint pupils (i.e., pretreatment controls) = 0 pts.; less than half-maximal dilitation = 1 pt.; at least half but less than maximal dilitation = 2 pts; and full dilitation = 3 pts. Pupil diameters were visualized using a penlight. The same person performed all eye examinations. After 14 hours the rats were allowed access to food and water. At 24 hours a final pupil examination was performed after which the rats were sacrificed by cervical dislocation. The small intestine was then examined for the regional distribution of polycarbophil gel.

RESULTS

The mydriasis scores for each treatment group are presented in table 1. Significant mydriasis was still evident at 12-14 hours in rats treated with the PC-atropine mixture. The pre-dried PC-atropine mixture exhibited a slightly (ca. 0.5 H) longer time to full effect and caused a slightly greater mydriatic effect over the test time, relative to the extemporaneously mixed PC-atropine treatment (table 1). In contrast, rats treated with atropine solution alone exhibited mydriasis for a maximum of 4 hours. No appreciable mydriasis was evident at 24 hours in any treatment group.

At autopsy, polycarbophil gel was found in the orad duodenum only. This was accompanied by an obstruction leading to profound gastric distention. PC gel was not found caudad to the duodenum. Atropine presumably impaired small intestinal motility to prevent aborad transit of the gel.

DISCUSSION

Incorporation of the atropine solution into the polycarbophil (PC) granules resulted in a profoundly systained mydriasis, relative to that seen after atropine solution alone. This was likely due to a continual leaching of the drug from the gel particles by gastric and duodenal secretions. The slightly greater mydriasis seen over time with the pre-dried PC-atropine mixture probably reflected a slower release of the drug than occured with the extemporaneously mixed

PC-atropine mixture. This would reflect the time needed to hydrate the pre-dried granules, dissolve the drug and then leach it from the gel. We conclude that the mydriatic effect of atropine can be sustained by using the atropine solution to hydrate the PC granules. Presumably this also applies to other water-soluble compounds such as cimetidine and various prostaglandins. In addition, it is possible that water-insoluble compounds (e.g., antacids) could be combined with PC to cause a prolongation of effect. In the case where the antacid $Mg(OH)_2$ is adsorbed to the PC granules, a slow gastric emptying of the PC granules (vide supra Chapter 4) might result in a prolonged gastric alkalinizing effect.

Table 1.

EFFECT OF POLYCARBOPHIL ON DURATION OF ATROPINE-INDUCED MYDRIASIS IN THE RAT.

	MEAN DEGREE OF MYDRIASIS AT SELECTED TIME INTERVALS (H)									
TREATMENT	1/2	1	2	4	6	8	10	12	14	24
PC/saline	0	0	0	0	0					
Atropine	3	3	3	1.3	0					
PC/A-wet	2.9	3	3	2.9	2.6	2.6	2.3	2	1.8	0.5
PC/A-dry	1	3	3	3	3	3	3	2.5	2	0.7

SCALE: 0: pinpoint

1: <1/2 max

2: >1/2< max

3: max pupil dilation

n: 6-8 rats per dose

atropine: 5 mg/Kg body weight