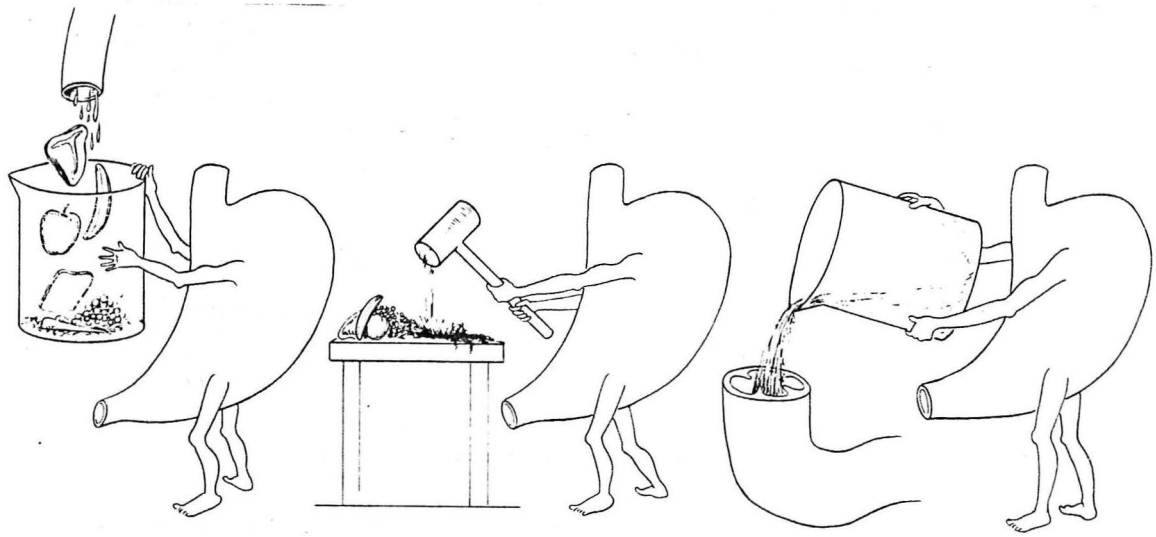
A DIGEST OF DIGESTION

MOTOR FUNCTION OF THE STOMACH IN HEALTH AND DISEASE



STORAGE PROCESSING EMPTYING

MEDICAL GRAND ROUNDS

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at Dallas

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INTRODUCTION

There are three interrelated motor functions of the stomach: (a) storage of ingested food, (b) processing of food by mixing food with gastric secretions and grinding solid food into small particles, and (c) timely emptying of gastric contents into the duodenum. These functions allow healthy individuals to eat large meals of varying composition rapidly and at erratic intervals, while presenting the absorptive surface of the intestine with a more continuous flow of nutrients. This optimizes absorption and minimizes large fluid shifts that might otherwise occur when a meal enters the intestine. Disruption of the orderly presentation of chyme to the intestine can lead to disabling symptoms and impaired nutrition.

Patients with disorders of gastric motor function present difficulties in recognition, diagnosis and management. They are difficult to recognize because their symptoms may be overlooked or attributed to other problems. They are difficult to diagnose because many widely available tests are insensitive and those few tests that are sensitive are not widely available. They are difficult to manage because therapeutic options are limited. Fortunately, new insights into the physiology of gastric motor function and new tests for identifying motor dysfunction now allow better understanding of these patients and hold the promise of more effective therapy for these conditions.

These Grand Rounds will highlight current concepts of the genesis and regulation of gastric motor function from the cellular level to the organ level with emphasis on the evolving understanding of gastric electrophysiology. In addition, this protocol will detail current methods of measuring gastric motor function, consider those conditions in which abnormal gastric motor function has been described, and discuss a clinical approach to patients suspected of having gastric motor disorders.

CELLULAR BASIS OF GASTRIC MOTOR FUNCTION

The initiation and coordination of movements of the stomach depend in a critical way on events at the level of the smooth muscle cell. Unlike skeletal muscle which is totally dependent upon extrinsic nerves for its activity, the basic activity of smooth muscle is largely independent of extrinsic innervation and arises in the muscle itself. Moreover, it has become clear that regional differences in cellular physiology may help to explain an apparent regional specialization of gastric motor function and the coordination of gastric motor activity.

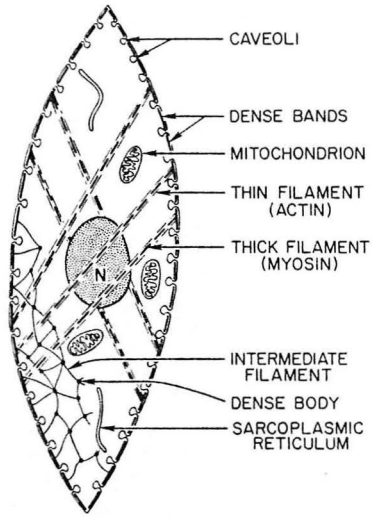


FIGURE 1. Schematic diagram of ultrastructural specializations of smooth muscle cell. N indicates nucleus.

Morphology. Under light microscopy, smooth muscle cells appear to be small, monotonously similar, fusiform cells. In contrast, electron microscopy reveals a number of functionally important structural specializations of the cytoplasm and cell membrane (1). As shown schematically in Figure 1, a network of filaments traverse the cell. These filaments are classified by size. Thin filaments, composed in part of actin, anchor to thickenings of the cell membrane called dense bands. Interposed among the actin fibers are thick filaments made of myosin. During contraction, it is thought that crossbridges form between actin and myosin causing the filaments to slide past each other, creating tension in the cell membrane and causing the cell to shorten. In addition to the thick and thin filaments, intermediate-sized filaments form a three-dimensional lattice between groups of actin and myosin filaments. The intermediate filaments join together at intracellular junctions called dense bodies and may form a sort of cytoskeleton for the smooth muscle cell (2). Thin filaments may also anchor to dense bodies but observations have been conflicting (1-3).

The cell membrane of the smooth muscle cell is specialized also. The total surface area of the cell is increased some 70% by invaginations of the cell membrane called caveoli (1). Caveoli come close to, but are not continuous with intracytoplasmic, membrane-lined interstices, the sarcoplasmic reticulum. The cell membrane of gastric circular muscle also has specialized junctions (gap junctions) with adjoining cells which serve two functions: to transmit tension and to provide low-resistance electrical pathways between cells. The first function allows summation of the mechanical effects of many cells and the second function allows local coordination of contraction and relaxation. Taken

together, these cell-to-cell junctions allow groups of smooth muscle cells to work in unison to produce macroscopic effects.

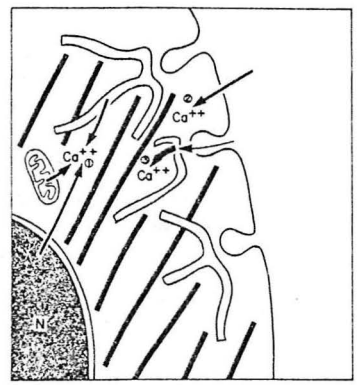


FIGURE 2. Postulated sources of contraction-activating calcium ions. Calcium may enter the vicinity of the contractile apparatus (heavy bars) from intracellular stores, such as the sarcoplasmic reticulum, mitochondria, or nucleus (N); from the extracellular space; or by a hybrid scheme in which small amounts of calcium entering from the exterior trigger release of large amounts of calcium from internal stores, such as the sarcoplasmic reticulum.

Biochemistry of contraction and excitation-contraction coupling.
Like skeletal and cardiac muscle, initiation of contraction in smooth muscle is the result of increased cytoplasmic calcium concentration (3,4). The source of this calcium is controversial (Figure 2). While it has been estimated that sufficient calcium is stored within the sarcoplasmic reticulum, mitochondria, and nucleus of the cell to activate all of the contractile filaments, it is likely that at least some (if not most) of the contraction-activating calcium moves across the cell membrane from the extracellular space and is then returned to the exterior when activation ceases (4-8). One hybrid scheme has small amounts of extracellular calcium entering the cell and triggering the release of much larger amounts of calcium from intracellular stores.

The mechanism by which elevated cytoplasmic calcium concentrations initiate contraction is thought to differ in smooth and in striated muscle (3,9-11). Although some controversy about this model remains, actin and myosin in striated muscle are thought to be ready to interact in the relaxed state but are prevented from doing so by the interposition of the protein, troponin, which sterically hinders the actin-myosin interaction. Calcium causes the removal of this

steric hindrance and contraction results. On the other hand, most investigators think that actin and myosin in relaxed smooth muscle are not ready to interact and that the light chains of myosin must first be phosphorylated (3,9-13). (In striated muscle, the light chains of myosin usually are already phosphorylated.) Calcium appears to initiate smooth muscle contraction by associating with a calcium binding protein, calmodulin, which then activates myosin light chain kinase, an enzyme which dramatically accelerates the phosphorylation of myosin. Phosphomyosin is then able to interact with actin, and contraction results (Figure 3). When cytoplasmic calcium levels fall, as the result of removal of calcium from the cytoplasm, myosin light chain kinase activity decreases and phosphomyosin is dephosphorylated by a phosphatase (myosin light chain phosphatase) and returned to its relaxed state. In some smooth muscles (gastric muscle has not been tested), myosin light chain kinase can itself be inactivated by phosphorylation (9-13), an event that would inhibit the ability of the cell to contract. This step appears to be mediated by cyclic AMP and controlled by a beta-adrenergic receptor (Figure 3). Beta-adrenergic activity may also increase the activity of myosin light chain phosphatase, relaxing the cell by transforming myosin back to its dephosphorylated (relaxed) form (14,15).

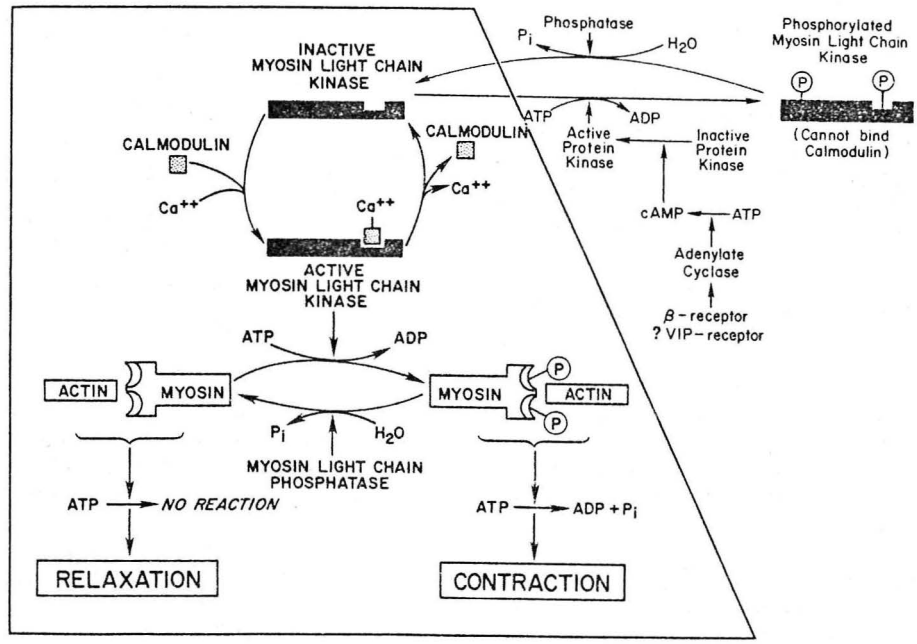


FIGURE 3. Biochemistry of smooth muscle contraction. As indicated within the borders, myosin phosphorylation by the enzyme myosin light chain kinase is a key step in the regulation of smooth muscle contraction. This enzyme is subject to reversible inhibition by a cyclic AMP regulated system as indicated outside the border.

Although much evidence has been adduced to support the concept that myosin phosphorylation regulates smooth muscle contraction, some recent observations do not support the theory. For instance, although the extent of myosin phosphorylation parallels tension development initially, in some tissues myosin phosphorylation declines with time even while tension is maintained (Figure 4) (16,17). This has suggested to some a relation of phosphorylation to the velocity of contraction rather than the force of contraction, and to others the existence of an energy-saving "catch" mechanism in vertebrate smooth muscle which would allow tension to be maintained without hydrolysis of additional ATP. Other schemes involving regulation of actin rather than myosin in a fashion analogous to skeletal muscle have been proposed by some investigators to account for discrepancies between observations and predictions of the myosin phosphorylation hypothesis (18).

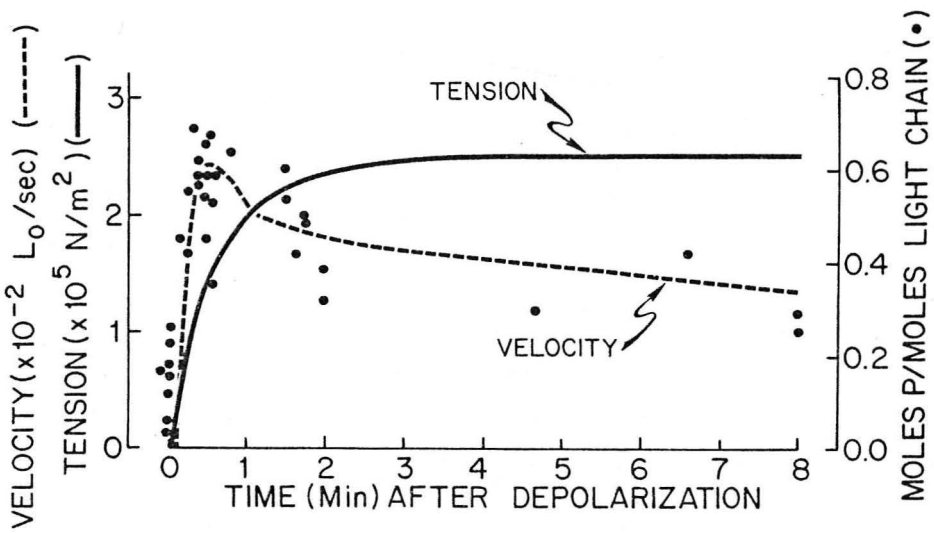


FIGURE 4. Time course of myosin light chain phosphorylation (dots), tension development (solid line) and shortening velocity (dashed line) in potassium-stimulated carotid media tissue. Phosphorylation appears to be more related to shortening velocity than to tension development. (Redrawn from Reference 16).

Cellular electrophysiology. The movement of calcium into the cytoplasm which triggers contraction is associated with and probably due to striking changes in membrane permeability and transmembrane electrical potential (4,19). Under resting conditions, ions such as sodium, potassium and chloride are distributed asymmetrically across the smooth muscle cell membrane as a result of selective membrane permeability and various active transport mechanisms. This asymmetrical distribution creates an electrical potential between the outer

(positive) and inner (negative) sides of the cell membrane (Figure 5). The precise mechanisms maintaining this transmembrane potential are still a matter of speculation but it is thought that active Na^+-K^+ exchange is involved (4). Depolarization due to changes in permeability and the movement of ions across the cell membrane is associated with activation of the contractile machinery. Repolarization is associated with relaxation.

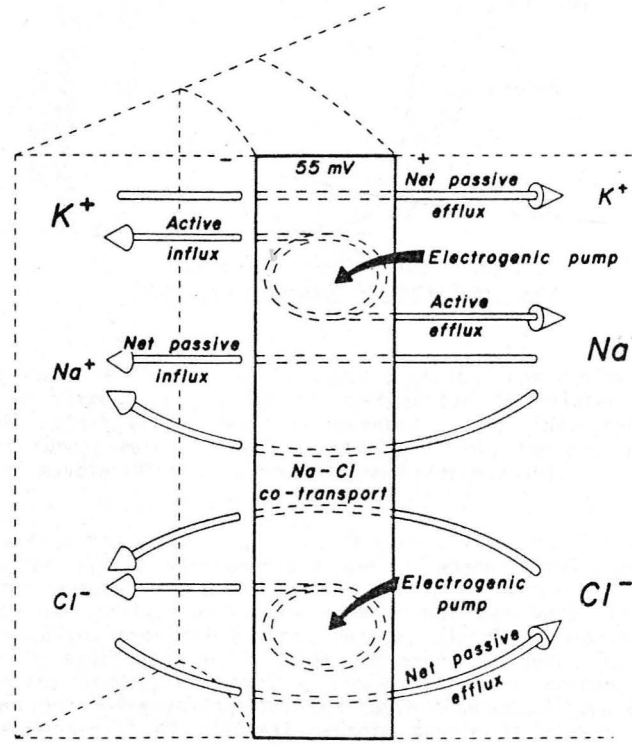


FIGURE 5. Postulated ion transport mechanisms in smooth muscle plasma membrane resulting in an asymmetric distribution of ions and a transmembrane potential difference (From Reference 19).

Experiments with canine gastric muscle in vitro indicate that transmembrane potential (measured with an intracellular electrode) is closely linked to the state of the contractile apparatus in the smooth muscle cell (19). This means that a plot of transmembrane potential versus muscle tension produces a smooth curve such that depolarization or repolarization produces predictable changes in muscle tension if the potential is above a threshold for mechanical activity

(Figure 6). Regional differences in these voltage-tension curves and in the electrophysiology of gastric muscle may explain functional differences between the proximal (fundus and proximal third of the corpus) and distal (distal corpus and antrum) portions of the stomach.

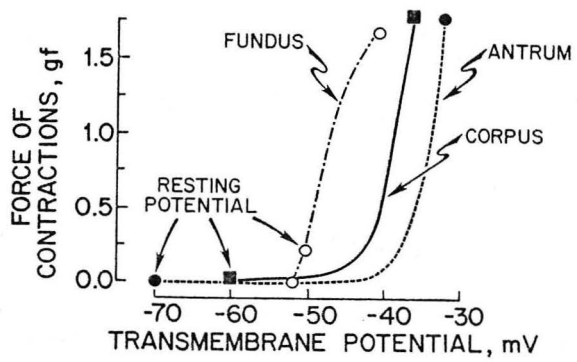


FIGURE 6. Voltage-tension curves for muscle strips from canine fundus, corpus, and antrum in vitro. The force of contraction is related closely to the transmembrane potential. Resting potentials are indicated. Mechanical threshold for fundic muscle is approximately -52 mV, for corpus muscle -45 mV, and for antral muscle -40 mV. (Redrawn from Reference 19).

In muscle from the proximal portion of canine stomach, resting transmembrane potential varies little spontaneously and is approximately -50 mV (19). In vitro studies indicate that transmembrane potential in muscle from the proximal human stomach is similar to canine stomach but may vary some spontaneously (20,21). In canine proximal gastric muscle, slight depolarization or hyperpolarization is associated with large increases or decreases in contractile force because the resting potential is already above the mechanical threshold on the steep portion of the voltage-tension curve (Fundus, Figure 6). Because the transmembrane potential of proximal gastric muscle is always maintained at a level above the mechanical threshold, this region of the stomach always has some degree of contraction and hence exhibits "tone" (Figure 7).

Muscle strips from the distal part of canine stomach display different patterns of electrical activity (19). In the distal corpus, the resting potential is more negative than that of the proximal stomach and is approximately 15 mV below the mechanical threshold (Figure 6). In addition, unlike the fundus, the transmembrane potential is not stable; spontaneous depolarizations which bring the membrane potential near the mechanical threshold occur every 12 sec (or every 20 sec in similar recordings in human beings). The ionic events underlying these spontaneous depolarizations are not fully understood. An additional depolarization (action potential) may be superimposed on the spontaneous depolarization bringing the transmembrane potential above mechanical threshold. This additional depolarization is thought to be due, in part, to an influx of

calcium ions (4,22). Following depolarization, repolarization occurs, usually interrupted by a prolonged plateau phase (Figure 7). The mechanical response to the initial rapid depolarization is usually brief and limited while the response to the plateau is variable, depending on the amplitude and duration of the plateau phase above the mechanical threshold.

The electrical behavior of canine antral muscle strips is, in general, similar to that of muscle from the distal corpus; however, there are several important differences. The resting transmembrane potential is more negative than more proximal regions and mechanical activity requires a greater depolarization (Figure 6). In addition, action potentials in the terminal antrum are distinguished by the presence of multiple spikes on the plateau phase (Figure 7). These spikes appear to intensify contraction. Thus, muscle from the distal corpus and antrum is distinguished from muscle in the proximal stomach by the presence of cyclical electrical activity and phasic contractions.

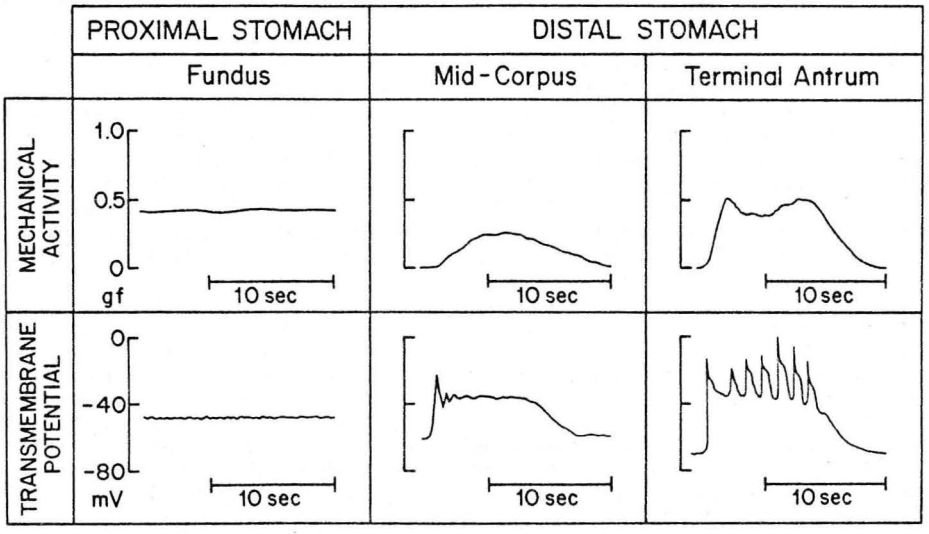


FIGURE 7. Transmembrane potential (lower tracings) and contractile force (mechanical activity; upper tracings) for canine gastric muscle in vitro. In the proximal stomach (left panels) electrical potential is above the mechanical threshold (-52 mV) and there is tonic contraction. In the distal stomach, contraction occurs when depolarization brings the transmembrane potential above the mechanical threshold (-45 and -40 mV, respectively). (Redrawn from Reference 19).

Muscle from the human pyloric sphincter, particularly muscle from the more distal part of the sphincter region, seems to behave somewhat differently than adjacent antral or duodenal muscle. Circular muscle in this region exhibits both tonic and phasic contractions in vitro (23). Transmembrane potential has not been recorded in such preparations and so it is uncertain whether or not this is due to a different pattern of electrical activity than other regions of the stomach.

Regulation of gastric smooth muscle cell function. Gastric smooth muscle cells have receptors for a wide variety of neurotransmitters, hormones and paracrine substances (19,24-29). These regulatory agents modify smooth muscle excitability and contractility and hence play an essential role in transforming the basic patterns of gastric electrical activity into the complex motor patterns that accompany ingestion of a meal and that occur during the interdigestive period. However, little is known about the detailed mechanisms by which these agents alter smooth muscle function and it has proved difficult to extrapolate what little is known to gastric function at an organ level. Moreover, the line between physiological and pharmacological effects is often poorly drawn.

Theoretically, regulatory substances might affect smooth muscle function in several ways. First, these substances might cause changes in transmembrane potential by affecting membrane permeability or the distribution of ions across the cell membrane and this, in turn, might lead to changes in contractility. One model for such an effect is the receptor-operated ion channel (26). Pharmacologists visualize the regulatory substance interacting with a receptor molecule on the cell surface which results in the opening of a transmembrane pathway for movement of a particular ion. If this movement results (either directly or indirectly) in depolarization, then the cell will be further along the voltage-tension curve and be more apt to contract or contract more strongly. An example of a stimulant thought to act in this fashion is acetylcholine. Application of acetylcholine to smooth muscle cells results in increased membrane conductance and in depolarization (30). As described in Figures 8 and 9, acetylcholine increases the amplitude and duration of the plateau potential and the force of contraction (31). Acetylcholine also increases the frequency of spontaneous depolarization, presumably by altering ionic movement (30). Gastrin and cholecystokinin have similar effects on electrical and mechanical activity in vitro in concentrations found in plasma postprandially (31-34). If interaction of the regulatory substance with the receptor-operated channel results in repolarization or hyperpolarization, then the cell is less apt to contract or will relax. Examples of inhibitors that may work in this way are norepinephrine (alpha-receptor) (31) and neurotensin (35) (Figures 10A and 10B). Secretin also decreases the amplitude and duration of the plateau potential and inhibits contraction but only at high concentrations (32).

A second mechanism must be invoked to account for regulatory substances that affect contractility without altering membrane potential. For instance, Figure 10C shows the effect of VIP on transmembrane potential and tension development. Contraction is markedly decreased even though membrane potential is unchanged (36). For this to happen, the normal events of excitation-contraction coupling described earlier must be disrupted. An example of one such mechanism is the inactivation of myosin light chain kinase by cyclic-AMP regulated protein kinase (Figure 3). Described originally as one possible mechanism for beta-adrenergic mediated smooth muscle relaxation, this may also be a mechanism by which VIP inhibits contraction without affecting membrane potential (37).

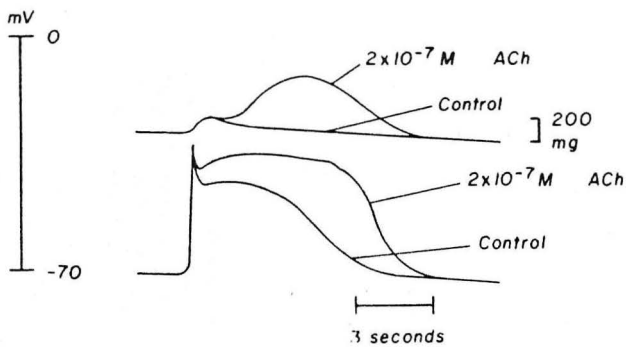


FIGURE 8. Effect of acetylcholine on transmembrane potential (lower curves) and mechanical activity (upper curves) in canine corpus in vitro. Increasing the plateau potential results in greater force generation. (From Reference 19).

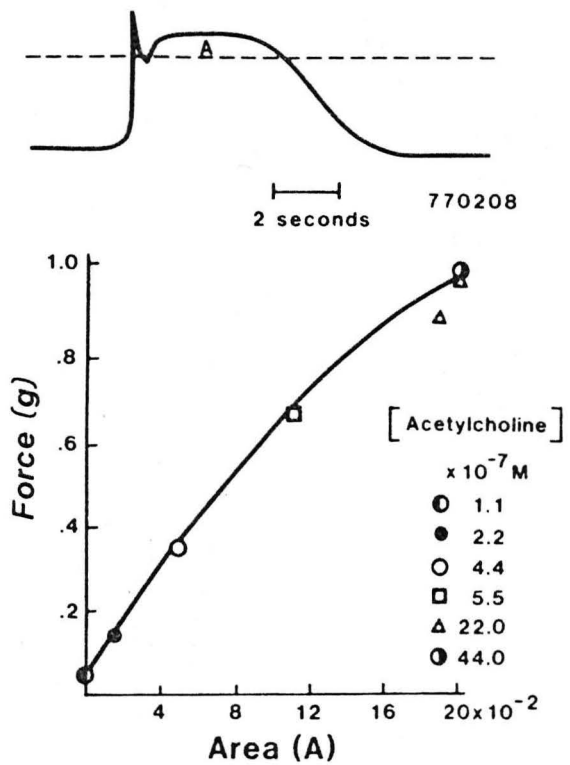


FIGURE 9. Relationship of plateau potential to force of contraction in gastric smooth muscle from canine corpus in vitro. At the top of this figure, the area (A) between the mechanical threshold (dashed line) and the plateau potential is indicated. At the bottom, a plot of area (A) versus force of contraction is shown. Area (A) was increased by exposing the tissue to increasing doses of acetylcholine. (From Reference 19).

It is likely that other mechanisms of action for endogenous regulatory substances remain to be discovered. Moreover, the effects of regulatory substances on the muscle cell membrane must be more clearly differentiated from effects of these substances on intrinsic nerves and paracrine regulatory mechanisms. When this is done, connections between events at the cellular level and organ function will be more readily understood.

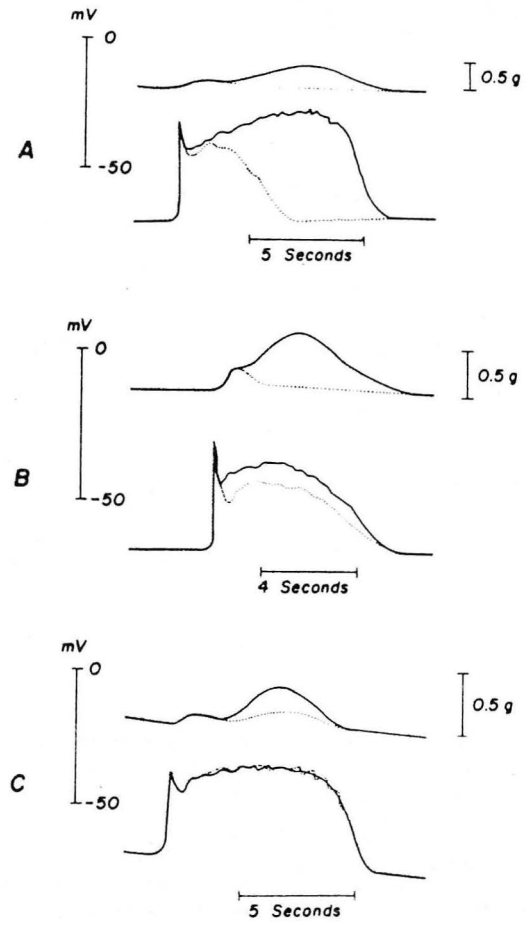


FIGURE 10. Effects of several inhibitory regulatory substances on mechanical activity (top tracings in each panel) and transmembrane potential (bottom tracings in each panel) in canine gastric muscle in vitro. In each panel, control records are shown as solid lines. Panel A: norepinephrine. Panel B: neurotensin. Panel C: vasoactive intestinal polypeptide. (From Reference 19).

RELATION OF CELLULAR ELECTRICAL PHENOMENA TO THE BASIC PATTERNS OF GASTRIC MOTILITY

Smooth muscle cells of the stomach do not contract and relax in isolation. Because of close electrical coupling via gap junctions, membrane potential changes in any single cell affect nearby cells. To understand the genesis of the basic motility patterns of the stomach, one must examine the electrical behavior of groups of cells in the different functional regions of the stomach: the proximal stomach (fundus and proximal third of the corpus) and distal stomach (the rest) (Figure 11).

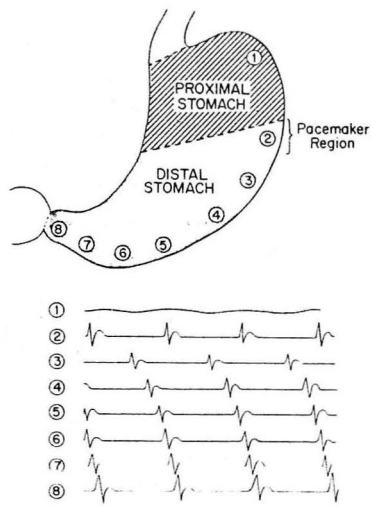


FIGURE 11. Electrical regions of the stomach and typical extracellular electrical recordings from various parts of the stomach. The proximal stomach, consisting of the fundus and the proximal third of the corpus, is electrically silent (tracing 1). The distal stomach shows cyclic triphasic potentials, the gastric slow waves, which originate in the pacemaker region along the greater curvature and then sweep distally toward the pylorus.

Proximal stomach. When extracellular electrodes (contacting large numbers of smooth muscle cells) are placed in the muscle of the proximal stomach, this area appears to be electrically silent: no phasic potential changes are noted (38,39). This is not surprising since, as was noted before, the transmembrane potential (measured by intracellular electrodes) in the proximal stomach is relatively constant, and contraction is unassociated with the presence of action potentials (19). Because of the electrical properties of its muscle, the basic motility pattern of the proximal stomach is simple: it has active tone which can be modified by relaxing or contracting in response to regulatory substances. Relaxation decreases intragastric pressure and allows for increases in gastric volume. Contraction has the opposite effects. Contractions of the proximal

stomach sometimes occur so rapidly that they appear to be phasic rather than tonic (40). However, these contractions are stationary: the proximal stomach does not have peristalsis.

Distal stomach. As we have seen, muscle from the corpus undergoes spontaneous slow depolarization which brings transmembrane potential near the mechanical threshold (19). This is reflected on extracellular recordings by a tri-phasic potential change (Figure 11). A small region of the mid-corpus high on the greater curve has the fastest frequency of spontaneous depolarization (3/min in human beings), and entrains the rest of the stomach to its faster rate. This region is known as the gastric pacemaker, and the triphasic electrical disturbance is known as the gastric slow wave. The details of the genesis and conduction of gastric slow waves are still controversial (41,42) but certain facts are known. Slow waves are not transmitted into the electrically silent proximal stomach, but do travel distally. Because they are transmitted much more rapidly around the circumference of the stomach than longitudinally, the slow wave becomes phase-locked around the circumference and travels distally, with ever increasing velocity, as a ring of partial depolarization. This depolarization brings the transmembrane potential closer to the mechanical threshold, and thus makes the occurrence of action potentials and contractions more likely. Because these slow waves are phase-locked around the circumference, are of fairly constant frequency and travel distally, they organize gastric contraction both spatially and temporally; contractions of the distal stomach are therefore ring-like and propagated distally in an orderly fashion. However, the slow wave only brings the muscle near the mechanical threshold; it does not insure that contraction will occur. Other factors, such as neural and humoral influences, determine whether a contraction will occur on a specific slow wave at a particular site in the distal stomach and, if so, its strength and duration.

MEAL-RELATED GASTRIC MOTOR FUNCTION

Let us now examine how the basic motor patterns of the stomach just described are modified by ingestion of a meal and how these modified patterns of motor activity explain the three main motor functions of the stomach: storage of food, processing of food by mixing and grinding, and timely emptying.

Storage of food.

One of the most important functions of the stomach is storage of food. Adequate storage not only allows ingestion of a large meal but also permits food to empty from the stomach at a slower rate than it is consumed. Thus, inadequate storage may not only result in early filling with consequent limitation of food intake but may also result in excessively rapid gastric emptying.

At the turn of the century, Cannon demonstrated the movements of the feline stomach by the then novel method of fluoroscopy (43). He described the fundus as "a most interesting active reservoir." Recent studies in man utilizing radioisotope-labelled meals have confirmed Cannon's observations and indicate that the bulk of the ingested meal is retained in the proximal stomach while a smaller amount is found in the distal stomach (44,45) (Figure 12). The amount in the proximal stomach declines as chyme is emptied, while the amount in the

distal stomach remains constant until emptying is nearly complete. Thus, the proximal stomach serves as a reservoir for the meal.

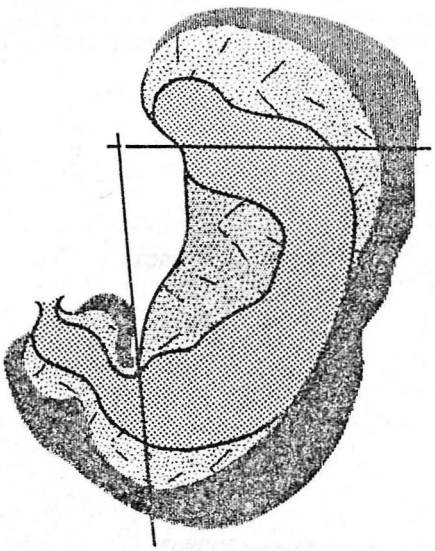


FIGURE 12. Radiographic silhouette of the stomach of a human being after ingestion of 60 ml (stippled area), 300 ml (intermediate zone), and 600 ml (dark outer area) of barium. Most of the ingested volume is accommodated in the proximal stomach. (From Reference 230).

Mechanism. The muscle of the proximal stomach and its basic pattern of motility are ideally suited for this storage function. As noted earlier, the proximal musculature has active tone which varies in response to changes in transmembrane potential (19). This can result in changes in the capacity of or pressure in the stomach. Thus, the proximal stomach is able to relax in order to accommodate a large volume of food and secretions without a corresponding increase in intragastric pressure (46). This phenomenon is known as adaptive relaxation and is the basis of the storage function of the stomach.

Regulation. Muscle tone in the proximal stomach is regulated by neural reflexes. Stretch receptors in the stomach wall initiate these reflexes and vagal fibers appear to be important both in completing the afferent limb and in mediating the efferent limb of these reflexes (46,47). However, local intramural reflexes probably are also important. Two vagal reflexes deserve special mention. The first, receptive relaxation, was described by Cannon and Lieb in 1911 (48). These investigators noted that the arrival of a food bolus in the

proximal stomach was preceded by gastric relaxation and that this effect could be eliminated by vagotomy (Figure 13). Little has been added to their description in the last 70 years. In particular, the identity of the inhibitory neurotransmitter released by the vagus nerve remains unknown. Neither acetylcholine nor norepinephrine appear to be likely candidates (49), but dopamine remains as a possible neurotransmitter for gastric relaxation (50). The other vagal reflex of note is gastric accommodation. Inflation of a balloon in the proximal stomach is followed by gastric relaxation such that intragastric

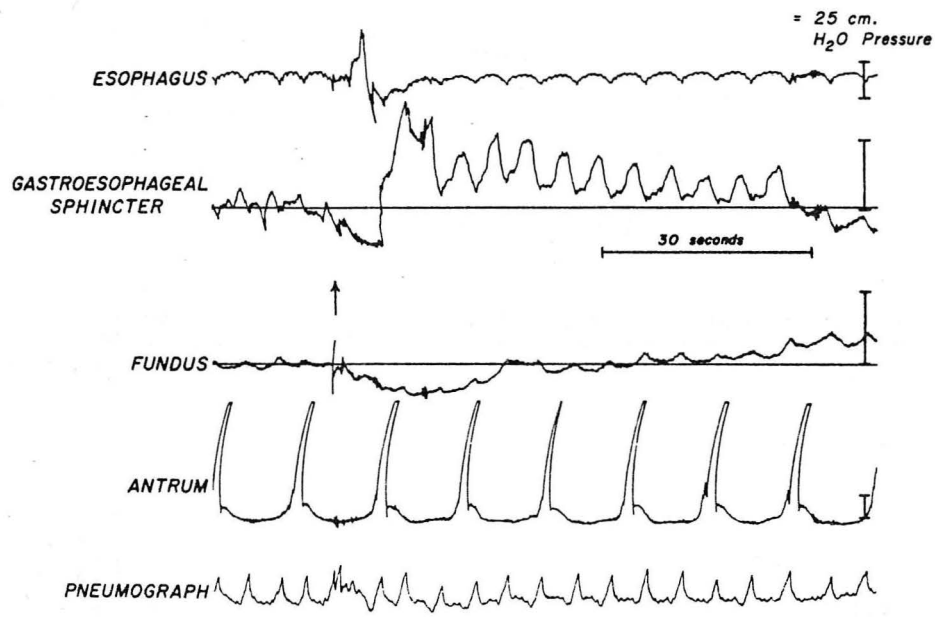


FIGURE 13. Receptive relaxation in dog gastric fundus during swallowing. Pressure records from the distal esophagus, gastroesophageal sphincter, gastric fundus and gastric antrum are shown. Note that the gastroesophageal sphincter and fundus relax (arrow) before arrival of the esophageal pressure wave at the gastroesophageal junction. (From Reference 230).

pressure remains nearly constant over a wide range of volumes (46,51) (Figure 14) Failure to accommodate allows increasing intragastric volume to dramatically increase intragastric pressure. This, in turn, can affect gastric emptying (52). For instance, vagotomy interrupts vagally-mediated gastric accommodation (46,51) and this is presumably the cause of precipitous emptying of a liquid meal in vagotomized subjects (Figure 15).

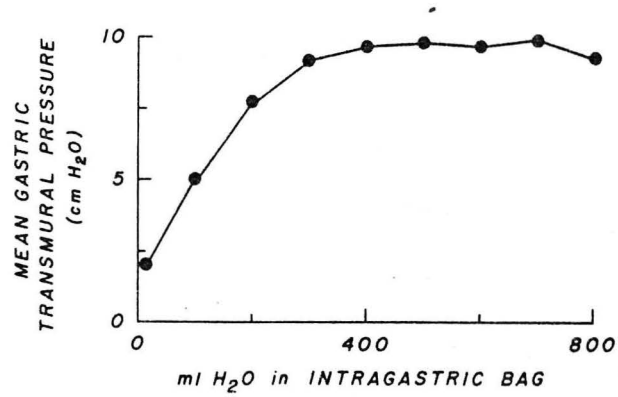


FIGURE 14. Accommodation of canine stomach to distention. Increasing volume from 400 to 800 ml did not result in any increase in gastric pressure. (From Reference 55).

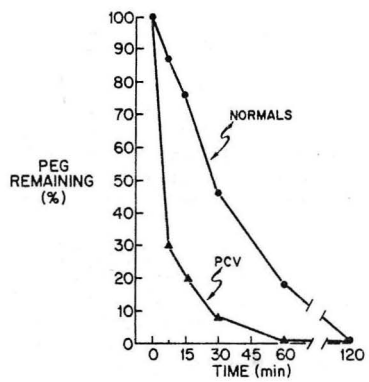


FIGURE 15. Polyethylene glycol (PEG) meal marker remaining in the stomach after intragastric infusion of a 700 ml amino acid meal in 10 normal subjects and 8 patients after parietal cell vagotomy (PCV). Early gastric emptying is extremely rapid in patients after vagotomy because of loss of gastric accommodation.

In addition to neural reflexes, gastric accommodation may also be regulated by humoral factors. Although several peptide hormones have been shown to affect intragastric pressure in dogs when an intragastric balloon was filled with 500 ml water (53,54) (see Table 1), only cholecystokinin has been shown to reduce intragastric pressure when given in doses less than the D_{50} dose for a known physiological effect (52).

TABLE 1.

PEPTIDES WHICH AFFECT INTRAGASTRIC PRESSURE IN DOGS WHEN AN INTRAGASTRIC BALLOON IS FILLED WITH 500 ML WATER (53,54)

Increase Intragastric Pressure
Motilin
Decrease Intragastric Pressure
Cholecystokinin*
Gastrin
Secretin
Glucagon
Gastric Inhibitory Polypeptide
Vasoactive Intestinal Polypeptide

*Decrease in intragastric pressure noted when given in doses less than D_{50} dose for known physiological effect (pancreatic enzyme secretion).

Processing of food.

Mixing and grinding of food take place in the distal stomach where powerful phasic contractions produce the forces necessary for these processes. Mixing and grinding increase the surface area of solid food particles allowing more efficient chemical digestion in the stomach and intestine. Together, these mechanical and chemical processes result in the production of relatively homogeneous chyme from the inhomogeneous mixed meal.

Mechanism. Mixing and grinding are the result of the interactions of the phasic myogenic electrical properties and the cone-like anatomy of the distal stomach. After a meal, gastric contractions in the capacious corpus of the stomach are usually of low amplitude and are almost never totally occlusive (55). These contractions, timed and spaced by the gastric slow wave, knead the solid food bolus and advance peripherally located food particles and gastric secretions toward the antrum (Figure 16). In the antrum, the lumen is narrower and contractions are stronger resulting in greater occlusion of the lumen and local areas of high pressure and of rapid flow of contents. Particles of food, advanced toward the pylorus by waves of contraction paced by the electrical slow wave, are subjected to increasing pressures and stream in jets antegrade through

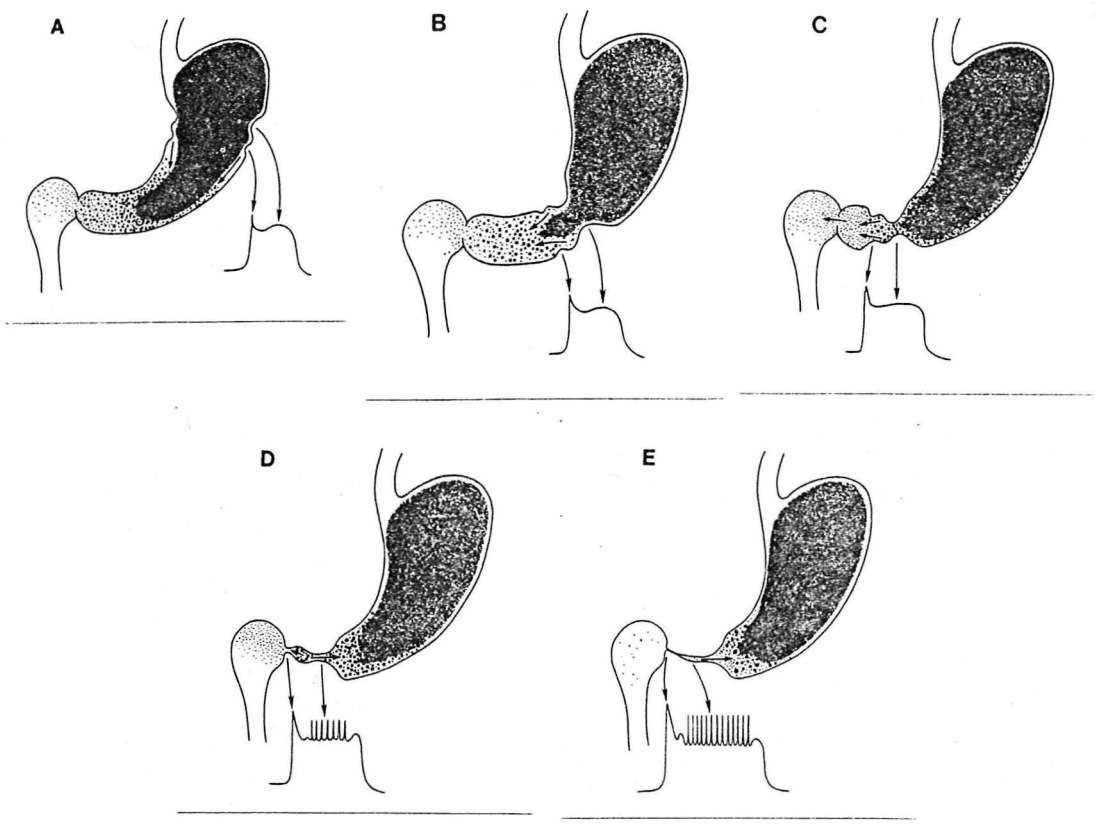


FIGURE 16. Schema of gastric processing and emptying of solid food. Intracellular electrical potentials, gastric contractions, and the effects of contraction on gastric contents are diagrammed. In Panel A, solid foods fills the proximal stomach and corpus. Gastric peristalsis begins with gentle contractions of the corpus. Paced by the electrical slow wave, the wave of contraction travels distally, compressing and kneading the solid food and breaking off small pieces (Panel B). These pieces are propelled into the antrum by progressively stronger waves, and small particles of food are accelerated through the still open pylorus by the force of contraction (Panel C). Antral contraction proceeds, and food is squirted through the narrowing pylorus and through the central orifice of the contraction wave (Panel D). The pylorus closes during the terminal antral contraction (Panel E), and all material is forced back to the corpus. Another wave then starts in the corpus, and the cycle is repeated. This pattern of activity results in the mixing and grinding of solid food and in the selective passage of small food particles into the duodenum.

the pylorus and retrograde through the small central lumen produced by the ring-like contraction. This continues until the contraction wave reaches the terminal antrum and the pylorus closes. Then, all material in the terminal antrum is rapidly expelled back toward the corpus as the terminal antral contraction

becomes totally occlusive. The high pressures and jet streams produced by this process produce collisions between particles and shearing forces that disrupt the larger particles. As the terminal antral contraction is occurring, another slow wave and contraction starts in the corpus and the cycle repeats itself.

A remarkable feature of this process is the efficiency with which solid food is dispersed into small particles and then emptied selectively. Ordinarily, gastric processing results in food particles no larger than 1 mm reaching the duodenum (56). The mechanism by which this is accomplished remains speculative. One possibility is that the food particles are accelerated by the force of contraction at a rate inversely proportional to their masses.* This would create a size/velocity gradient in the antrum with smaller, more rapidly moving particles moving ahead of larger, slower particles. Particles would empty from the stomach as long as the pylorus remains open. However, the onset of the terminal antral contraction triggers pyloric closure, trapping the more slowly moving particles in the antrum. Thus, the smaller, faster particles would be preferentially passed into the duodenum and the larger, slower particles would be retained in the stomach for further grinding (Figure 17). Other schemes have been described (19,55).

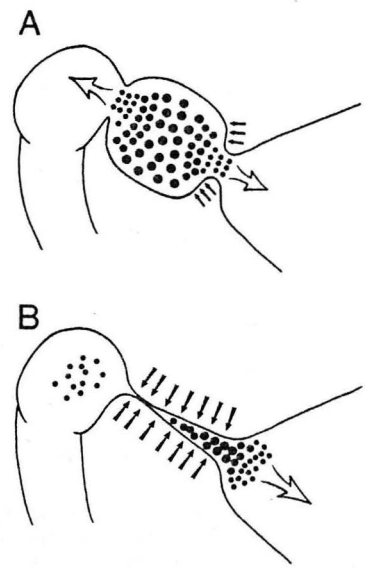


FIGURE 17. Schematic diagram illustrating hypothetical mechanism of sieving solids and selectively retaining larger pieces for further grinding. In Panel A a peristaltic wave is approaching the terminal antrum. Smaller particles are preferentially accelerated through the open pylorus and through the advancing peristaltic ring contraction. In Panel B pyloric closure forces all material to be retropulsed.

*Given force, F = ma, mass times acceleration, and assuming that the only important force acting on the food particle is that due to the difference in pressure between the front and back of the particle, dF = m da = A dP, where A = cross-sectional area of the particle and dP = difference in pressure on either side of the particle. Substituting dv/dt for da and rearranging, we get dv = dP dt A/m, the velocity is inversely proportional to the mass of the particle. Since the ratio of cross-sectional area, A, to the mass, m, is constant (for a spherelike particle of uniform density) and equal to 3/4r, dv = 3 dP dt/4r, the velocity of the particle is inversely proportional to its radius.

Regulation. Regulatory factors for mixing and grinding are poorly understood. Neural mechanisms are probably important. Studies in animals indicate that vagal stimulation can increase the amplitude of contraction in the distal stomach (57) and gastric distention stimulates antral motility by a vagally-mediated reflex (58). Conversely, truncal vagotomy weakens antral contractions and disrupts terminal antral contraction (59).

Meal stimulated hormone release may also be an important regulator of mixing and grinding. The best documented example is gastrin. Administration of gastrin to dogs in physiological doses causes the frequency of the electrical slow wave to increase by 20% and causes action potentials to occur on a greater proportion of slow waves in the distal stomach (60). Other gastrointestinal peptides that may affect motility in the distal stomach are listed in Table 2.

TABLE 2.

PEPTIDES WHICH ALTER DISTAL STOMACH MOTILITY (55).

Augment contractions
Gastrin
Cholecytokinin
Motilin
Inhibit contractions
Secretin
Glucagon
Gastric Inhibitory Polypeptide
Vasoactive Intestinal Polypeptide
Somatostatin

Other factors that may regulate the processing of food are the mechanical properties of the gastric contents. A recent study in dogs suggests that the depth of indentation produced by antral contraction depends on the viscosity of gastric contents: the more viscous the luminal contents, the shallower the contraction and the greater the diameter of the central lumen (61). This would allow for greater retrograde flow with more viscous contents. The mechanism sensing viscosity is unknown.

Gastric emptying.

The most studied motor function of the stomach is gastric emptying. The transfer of material from the stomach to the duodenum requires the coordination of the proximal stomach, distal stomach and duodenum (55). Because of this, it is closely linked to the other motor functions of the stomach and occurs

simultaneously with them. Indeed, gastric emptying is the result of the same basic motility patterns as these other functions.

Gastric emptying of liquids is somewhat different than the emptying of solids. Accordingly, the two types of meals will be discussed separately.

Mechanism of emptying: liquids. Liquids leave the stomach in response to the overall gastroduodenal pressure gradient as modified by resistance to flow in the gastric outlet and duodenum (55). Intragastric pressure is determined by the tonic contraction of the proximal stomach and can be regulated over a range of some 30 mmHg, although intragastric pressure is usually quite low. The overall gastroduodenal pressure gradient also depends on intraduodenal pressure which is determined by phasic contractions of the duodenum. At times duodenal pressure may be above intragastric pressure (for instance, during a duodenal contraction). At these times gastric emptying cannot take place and duodeno-gastric reflux is possible. Gravity may also alter the gastro-duodenal pressure gradient and contribute to the egress of rapidly emptying liquids such as isotonic saline solution, but gravity has little or no effect on more slowly emptied liquid meals (62).

The role of resistance factors in modifying gastric emptying of a liquid meal is controversial. Resistance to emptying is due to antral and pyloric contraction and also to the resistance of the small intestine to filling (63). Antral contractions are not remarkably strong after ingestion of a liquid meal (64,65) and even when stimulated (by electrical vagal stimulation in animals) do not slow gastric emptying (57). The role of the pylorus in modifying gastric emptying of liquids is also debatable. Although in some studies the pylorus appears to be a tonic high pressure zone (66-68), other studies have not confirmed this (69,70). Some authors contend that pyloric muscle may ordinarily be relaxed, contracting only when activated by the antral slow wave during terminal antral contraction (55). It would thus be functionally integrated with the antrum during the post prandial period and not an independent structure. Against this concept is the particularly rich innervation at the pylorus (especially VIP [71] and enkephalinergic [72] neurons in the cat) and the unique pattern of responses to gastrointestinal peptides characteristic of the pylorus (55,68), which suggest independent regulation. Moreover, human pyloric sphincter muscle in vitro appears to generate both phasic and tonic contraction (23). However, it seems likely that pyloric resistance is not solely responsible for the regulation of liquid emptying because animal studies indicate that propping the pylorus open with a cannula does not accelerate gastric emptying (73) (Figure 18). Also, while pylorectomy in dogs increased the rate of

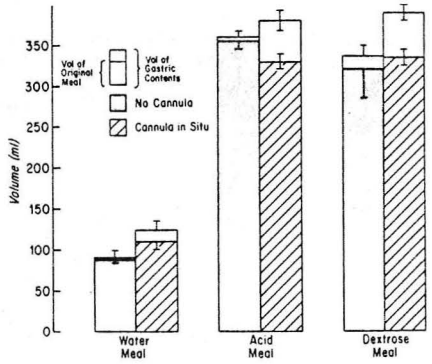


FIGURE 18. Effect of keeping the pylorus open with a pyloric cannula in dogs. Volume refers to gastric volume 30 min after infusion of a 480 ml test meal. The volume of the original meal remaining was not significantly different with or without a pyloric cannula in place. (From Reference 73).

transfer of material both from stomach to duodenum and from duodenum to stomach, this increased to-and-fro movement did not alter the net transfer to material from the stomach to the duodenum after a slowly emptied test meal (74). On the other hand, the emptying of a rapidly emptying liquid was accelerated by pylorectomy (75). All in all, pyloric motor function may have more to do with the prevention of duodeno-gastric reflux (55,66,73,74), and the sieving of solids (55,75) than with gastric emptying of liquids. Resistance of the small intestine to filling may be a more important determinant of the rate of gastric emptying but is only beginning to be investigated (63,76). In summary, it seems likely that antropyloric resistance is not an important regulator of liquid emptying but that proximal stomach tone or intestinal resistance is what is modified to regulate liquid emptying.

Mechanism of Emptying: Solids. The emptying of solid food is intimately connected with the process of mixing and grinding. As discussed earlier, solid food is disrupted into small particles by antral contractions (Figure 16). Small particles pass into the duodenum before terminal antral contraction and pyloric closure. Larger particles are retained in the stomach for further processing. Indigestible constituents of solid food (such as seeds) are also retained within the stomach and are emptied by a special mechanism during the interdigestive period (see below) (55).

Evidence for close linkage between gastric processing (mixing and grinding) and emptying of solids comes from several sources. Studies in dogs indicate that the emptying of radiolabelled chunks of solid food is slower than simultaneously ingested liquids (77,78) but is identical to the liquid phase if the solid food is homogenized before ingestion (77) (Figure 19 and 20). Moreover,

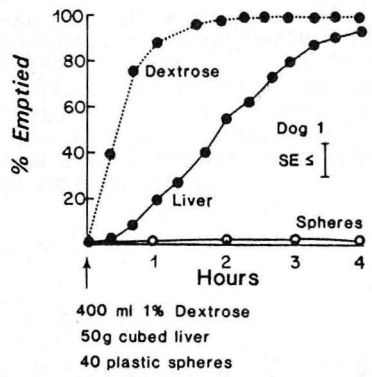


FIGURE 19. Gastric emptying of dextrose solution, cubed liver and indigestible plastic spheres in a dog. The liquid empties quickly, solid at a relatively constant rate and spheres not at all over the four hours after ingestion of the meal. (From Reference 55).

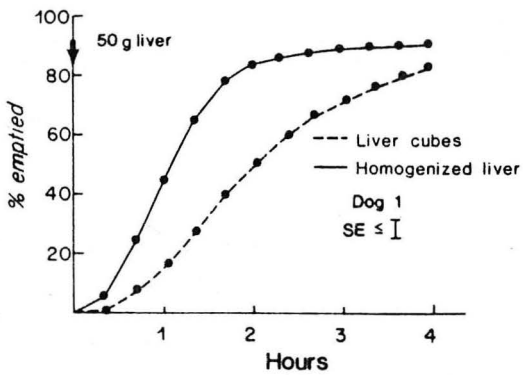


FIGURE 20. Gastric emptying of liver cubes (dashed line) in a dog differs from that of homogenized liver, which resembles the liquid emptying pattern shown in the preceding figure. (From Reference 55).

the rate at which solid food is emptied from the stomach depends on the original size of the ingested solids: dispersed liver (0.25 mm particle size) empties faster than cubes of liver (1 cm) in dogs (78) and in normal human beings (79,80) (Figure 21). Almost no food particles larger than 2 mm were found in duodenal contents in dogs fed 1 cm liver cubes and 97% of the liver particles in the duodenum were less than 0.5 mm in size (78). Limited studies in human subjects have been consistent with these findings (56,79-81). Thus, the emptying of digestible solids from the normal stomach depends on the rate at which such solids are reduced in size or solublized. The importance of normal anatomy for this process is illustrated by two studies in human beings after gastric surgery. Vagotomy and antrectomy allowed the precipitous emptying of larger sized particles of food and the earlier emptying of indigestible markers as compared to non-operated subjects (80,82).

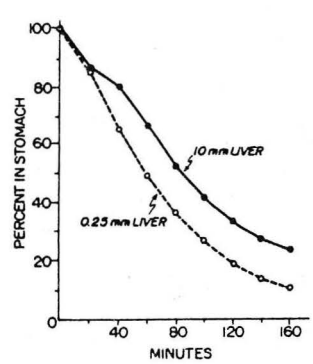


FIGURE 21. Emptying of 0.25 mm and 10 mm liver cubes in human beings. The smaller pieces empty more rapidly than the larger pieces of liver. (From Reference 79).

Patterns of Emptying. In general, liquids empty from the stomach at a rapid rate. After a brief period of early emptying during which the emptying rate may be faster or slower than the rate ultimately achieved, emptying rate (in ml/min) is proportional to the volume remaining in the stomach: the larger the volume, the faster the rate of emptying of the liquid test meal (83). While this suggests a log-linear relationship, some investigators (84) have claimed a closer fit to a linear relationship when the square root of the gastric volume is plotted against time (Figure 22).

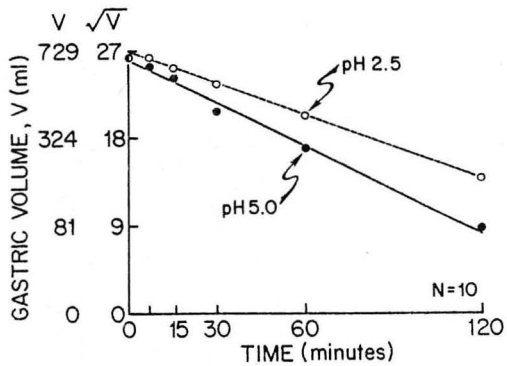
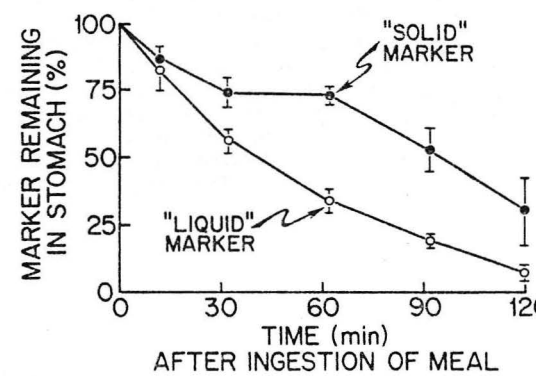


FIGURE 22. Mean gastric volume as a function of time after infusion of a 700 ml mixed amino acid meal, adjusted to and maintained at pH 5.0 or pH 2.5, in ten normal subjects. Plot of the square root of gastric volume versus time closely approximately a straight line.

Solids, on the other hand, empty from the stomach at a relatively constant (zero order) rate regardless of the amount ingested or the amount of liquid ingested along with the meal (Figures 19 and 23) (83,85). This pattern seems to

FIGURE 23. Gastric emptying of solid and liquid phase meal markers in human beings. (From Reference 62).



be due to the requirement for processing in the distal stomach prior to the emptying of solid food and the likelihood that this processing occurs at a relatively fixed rate. However, the emptying rate of solids can be altered by the character of other ingested substances such as fat (85) or hypertonic fluid (77).

Regulation of Gastric Emptying. Gastric emptying is regulated so as to provide a relatively constant flow of nutrients into the small intestine. It is postulated that physical and chemical characteristics of chyme activate specific receptors in the duodenum and jejunum that modify gastric motor activity by neural and/or humoral mechanisms (86). However, such receptors have yet to be identified anatomically and the mechanisms by which receptors modify gastric motor activity have been poorly characterized. In general, activation of these putative receptors results in slower gastric emptying than would otherwise be the case. In addition to receptor-mediated regulation, it is likely that gastric emptying is closely regulated by neural and humoral responses to the ingestion of a meal.

One of the key physical properties of chyme sensed by the small bowel receptor mechanism is osmolality. Gastric emptying slows as the osmolality of a meal is increased above isotonicity (86). (For a few substances, hypotonic solutions also slow emptying [55]). This receptor mechanism appears to be located in the duodenum rather than in the stomach or jejunum in humans (87). J.N. Hunt has speculated that the lateral intercellular space of the duodenal mucosa is the site of the receptor mechanism and that changes in the volume of this space initiate the regulation of gastric emptying, but these contentions are unproven (88,89) (Figure 24). The osmoreceptor is thought to be extraluminal because it not only senses the osmolality of chyme in the lumen but also senses the potential osmolality produced by hydrolysis of complex proteins and carbohydrates into amino acids (90) and simple sugars (86). This is particularly important in the regulation of caloric load to the intestine since both carbohydrate and protein are hydrolysed into simple sugars and amino acids of roughly the same size with roughly the same caloric value, 4 kcal/gm. Thus, by regulating the osmotic load to the duodenum, this mechanism results in regulation of the caloric load of carbohydrate and protein presented to the intestine.

The other caloric source, fat, also regulates gastric emptying. Receptors sensitive to fatty acids, particularly those with 12-14 carbon atoms, are found in the duodenum and perhaps in the jejunum (86). These receptors also slow gastric emptying. It is thought that the inhibition produced by the fatty acid receptor is such that equicaloric amounts of fat, carbohydrate and protein are emptied at similar rates (88,89,91). However, this proposition has not been tested prospectively. It is clear that the slowing of emptying by fat is due to hydrolytic products of fat digestion since a non-hydrolyzable fat analog (sucrose polyester) does not delay gastric emptying (92).

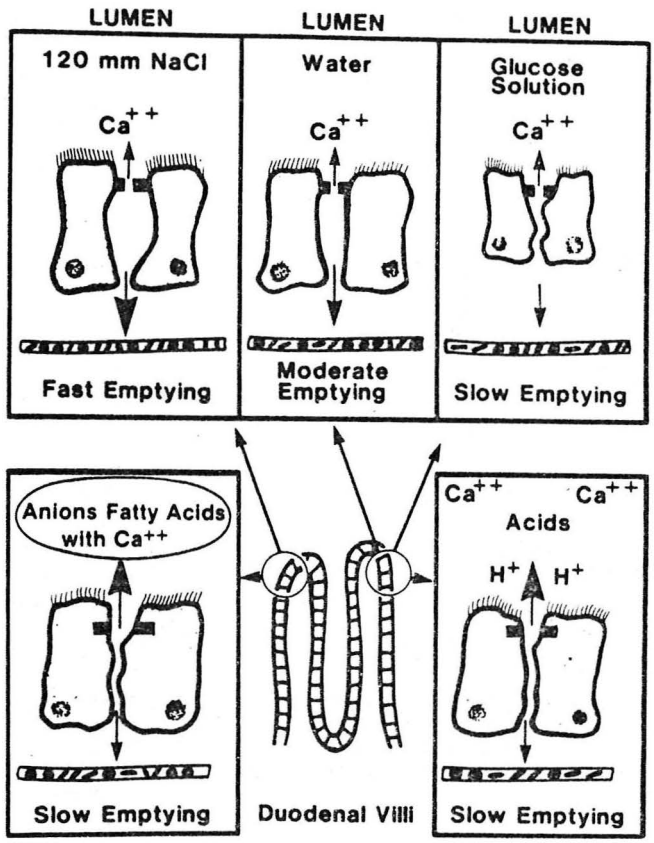


FIGURE 24. J.N. Hunt's hypothesis that the lateral intercellular space between duodenal mucosal cells is the transducer for regulation of gastric emptying by chyme. Maximal volume of spaces is condition for minimal slowing of gastric emptying (upper left panel). Stimuli that reduce volume of spaces by osmotic effects (upper right panel) or by displacing calcium and opening tight junctions (lower panels) slow gastric emptying. (From Reference 89).

The small intestine also senses luminal acidity and slows gastric emptying as acidity increases (Figure 25) (86). For liquid test meals in normal subjects, gastric emptying is fastest for meals at pH 7 and progressively slows as pH falls (93). However, the acid sensing mechanism not only responds to pH, but also to the species of anion present: the effectiveness of acids in slowing gastric emptying is inversely proportional to the square root of the molecular weight (93). (Figure 26). The acid receptor may mediate its action by a humoral mechanism ("enterogastrone") but the speed with which intraduodenal acid infusion slows emptying suggests a neural reflex mechanism.

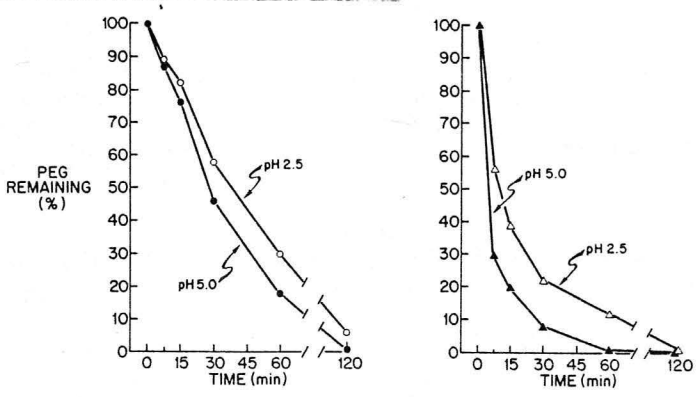


FIGURE 25. Polyethylene glycol (PEG) meal marker remaining in the stomach after intragastric infusion of a 700 ml amino acid meal adjusted to pH 5.0 or pH 2.5 in normal subjects (left panel) and patients after parietal cell vagotomy (right panel). Acidification of the meal slows emptying in both normal individuals and those with vagotomy.

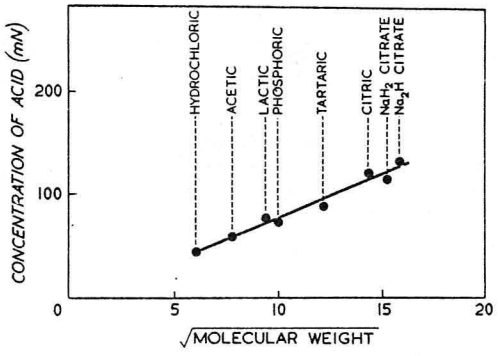


FIGURE 26. Concentration of acid necessary to produce an equal slowing of gastric emptying as a function of the square root of molecular weight. (From Reference 86).

In addition to receptor-activated neural reflexes, nerves supplying the stomach mediate central nervous system regulation of gastric emptying (94). Studies in anesthetized animals suggest that ablation or electrical stimulation of several regions of the cerebral cortex, brainstem or spinal cord can affect gastric motility. These effects are mediated by the parasympathetic and sympathetic divisions of the autonomic nervous system. Central nervous system effects on emptying of a test meal have been less well studied than effects on gastric contractions. One study in healthy volunteers showed that labyrinthine stimulation delayed gastric emptying and markedly altered duodenal motor activity (95). Electrical vagal stimulation can speed the emptying of a test meal in animals (57), but physiological central nervous system stimulation by sham feeding has little or no impact on the emptying of meals in human beings (Figure 27) (96). Vagotomy slows the emptying of solids, probably by decreasing the force of antral peristalsis, but speeds the emptying of liquids by reducing the reservoir capacity of the proximal stomach (94). Sympathectomy (94) or treatment with beta-adrenergic antagonists (97) accelerates emptying, suggesting that gastric emptying is normally subject to some degree of sympathetic inhibition. Infusion of dopamine delays the emptying of liquids, presumably by decreasing intragastric pressure (98).

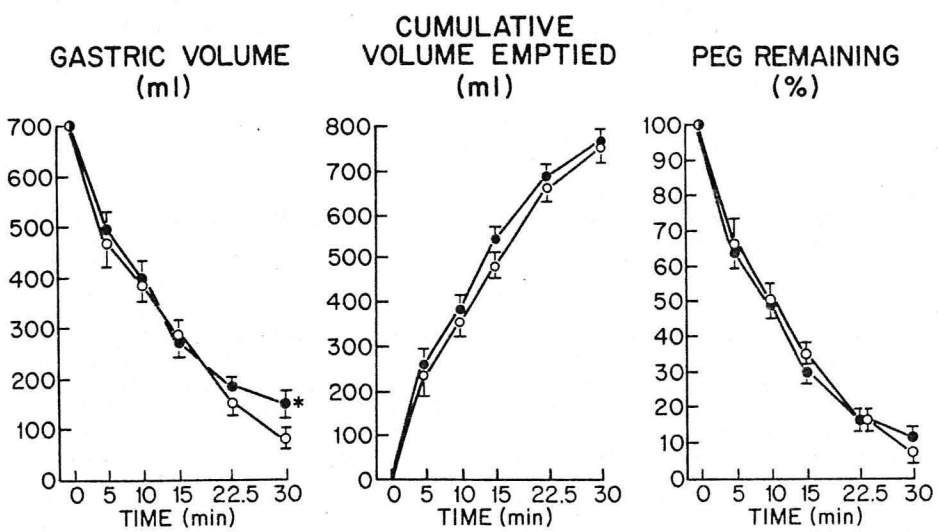


FIGURE 27. Mean gastric volume, cumulative volume emptied and PEG remaining in the stomach after intragastric infusion of 700 ml saline in 8 subjects with (filled circles) or without (open circles) concurrent sham feeding. Sham feeding had little effect on the emptying of saline from the stomach. (From Reference 96).

Gastrointestinal peptides may also have a substantial (though as yet unproven) role in the regulation of gastric emptying. Gastrin (99), cholecystokinin (100), somatostatin (101), motilin (102), neurotensin (103), and bombesin (104) have been reported to slow gastric emptying of various test meals in human beings. Conflicting results have been reported for somatostatin (105) and motilin (106,107), in man. The physiological relevence of these studies is uncertain. Cholecystokinin has been claimed to be a physiological regulator of gastric emptying in dogs (108), but in most human studies with this and other peptides, pharmacological rather than physiological doses were administered. Moreover, test meals varied in size and composition from study to study and this may have an important influence on the results of these experiments. For instance, in one study, motilin was found to speed the emptying of a glucose meal but had no effect on the emptying of a cream meal (107). It has also proved difficult to predict effects of peptides on emptying based on the pharmacological effects of these peptides on gastric motility or on smooth muscle contractility. For instance, both gastrin (99) and secretin (100) slow gastric emptying, even though they have opposite effects on antral motility (increased and decreased antral contractions, respectively [55]). Much more remains to be learned about peptide effects on gastric emptying but development of this knowledge will require careful studies with physiological doses of these agents and standard test meals. In one such recent study, "physiologic" doses of secretin but not cholecystokinin delayed the emptying of a saline meal in humans (109).

INTERDIGESTIVE GASTRIC MOTOR FUNCTION

During fasting the stomach is not continuously quiet. Cyclical bursts of occlusive contractions occurring on every slow wave recur approximately every two hours (55,110). These bursts usually originate in the distal esophageal sphincter and stomach (55,111,112) and then pass across the gastroduodenal junction and down the intestine to the colon. An increase in gastric and pancreatobiliary secretion precedes each burst in humans (113). Studies in animals indicate that these contractions are occlusive, and that they sweep all gastric contents, including secretions and indigestible solid materials, ahead of them. Unlike meal-related gastric motor function, the advancing contractions do not cause pyloric closure and thus all the gastric contents are emptied from the stomach over a short interval (55,114). These bursts of contractions are known as the "interdigestive myoelectric complex" and have been fancifully labelled the "interdigestive housekeeper" because of their ability to sweep debris along the gut (115). While this transport function has been clearly shown in animals (114) (Figure 28), it has not yet been demonstrated (although it seems likely to occur) in humans. If it does occur, disturbance of the interdigestive myoelectric complex might be associated with retention of undigestible material in the stomach and, perhaps, bezoar formation (116).

Regulation of Interdigestive Myoelectric Complex. Fasting motor activity begins at varying times after ingestion and emptying of a meal and then occurs at more or less regular intervals until the next meal is eaten (117). Ingestion of a meal disrupts the interdigestive myoelectric complex within minutes. The signals that turn fasting motor activity on and off are not fully understood but probably include both humoral and neural mechanisms. Most interest has focused on the peptide, motilin. Blood levels of motilin rise immediately before the

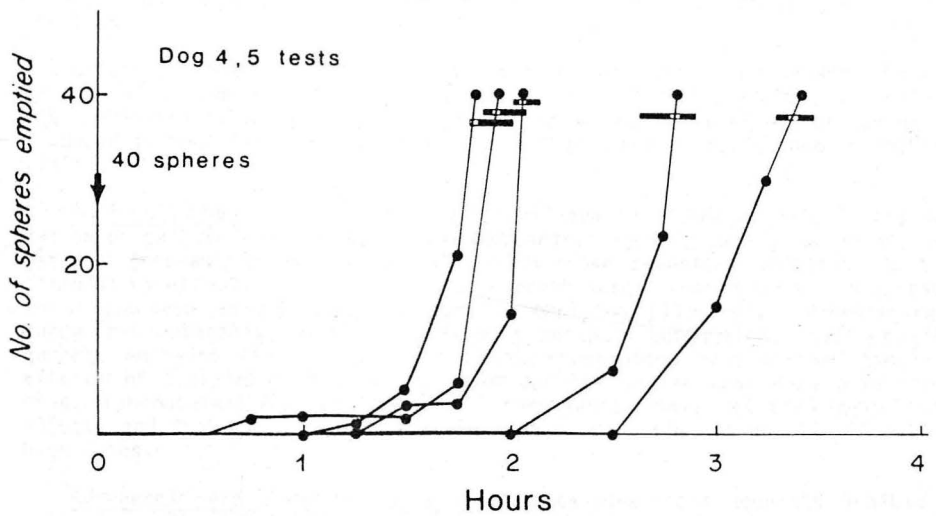


FIGURE 28. Pattern of canine gastric emptying of plastic spheres (diameter, 7 mm) during fasting. Occurrence of Phase III of the interdigestive motor complex is indicated by the horizontal bars. (From Reference 55).

onset of peak interdigestive motor activity ("Phase III") in man (118,119) and dog (120-122). Infusion of exogenous motilin during a quiescent phase of the interdigestive period induces premature myoelectric cycles that are identical to spontaneously generated cycles (118,121,122). Thus, it is possible that motilin release is the physiologic signal initiating interdigestive myoelectric complexes. On the other hand, migration of the activity front along the stomach and intestine appears to require intact intrinsic and extrinsic innervation (55). Feeding promptly disrupts the fasting pattern as does sham feeding (123) or administration of exogenous gastrin (124,125) insulin (125), somatostatin (122,126), and cholecystokinin (127). Vagal integrity facilitates the change from the fasting to the fed pattern (124). Whether eating a meal blocks fasting motor activity by increasing circulating levels of these peptides, by reducing plasma motilin levels, or by altering neural activity is unknown.

DRUGS AND GASTRIC MOTOR FUNCTION

Many drugs alter gastric motor function. These alterations sometimes produce symptoms such as nausea and vomiting, which, if unrecognized as being drug-related, may lead to the suspicion that the patient has a primary gastric disorder. Drug-induced changes in gastric motor function may affect the results of diagnostic tests such as the glucose tolerance test (128) or may alter the

bioavailability of the drug itself or other drugs taken at the same time (129). Clinically, opiates, anticholinergics and psychotropic drugs cause the most severe problems, but other types of agents also may affect gastric motor function.

Opiates. Morphine inhibits the emptying of both liquid meals (130) and solids (131) from the stomach. Curiously, in the latter study (131) naloxone also inhibited solid emptying. The mechanism by which the effect of morphine is produced is uncertain. One possibility is that duodenal resistance is increased (132).

Anticholinergics. Muscarinic receptors have an important role in the activation of gastric smooth muscle. Antimuscarinic agents, such as atropine, inhibit the interaction of acetylcholine with these receptors and thus limit the stimulatory effects of acetylcholine on smooth muscle contraction. This results in a decrease in the rate of gastric emptying (133,134). Pirenzepine, a muscarinic antagonist specific for the M_1 receptor population, does not affect gastric emptying (133), suggesting that M_2 receptors mediate the stimulatory effects of acetylcholine. It is important to realize that many psychotropic drugs (phenothiazines, tricyclic antidepressants) have anticholinergic side-effects and that these agents can cause gastric stasis, especially if given in high doses.

Adrenergic and Dopaminergic Drugs. Beta-adrenergic agonists inhibit and beta-adrenergic antagonists, such as propranolol, accelerate gastric emptying (97). Dopamine (98) and levodopa (135) slow emptying, probably by inducing proximal gastric relaxation (50). A relationship between gastric emptying and systemic availability has been suggested for l-dopa (129).

Histamine and H_2-receptor antagonists. Results of studies of gastric emptying after H_2-receptor blockade have been inconsistent. An acute oral dose of cimetidine had no effect on gastric emptying of a mixed liquid-solid meal, but there was a positive correlation between the emptying rate of the liquid component of the meal and the rate of absorption of cimetidine during the first hour (136). In another study (137), long-term treatment with cimetidine accelerated the emptying of the solid but not the liquid components of a test meal. This returned to normal after stopping therapy. In contrast, the new H_2-receptor antagonist, ranitidine, delayed gastric emptying of solids (138), suggesting that it is not H_2-receptor blockade per se but rather some other characteristic of these drugs that affects gastric motor function. This is also suggested by studies in rats in which histamine, but not the H_2-agonist, dimaprit, inhibited emptying, an effect which could be blocked by H_1-receptor antagonists but not by H_2-receptor antagonists (139).

Other drugs. Antacids appear to slow gastric emptying (140,141), an effect which enhances their ability to neutralize gastric acid. Aspirin delays gastric emptying (142), an effect that may be related to inhibition of prostaglandin synthesis, since exogenous prostaglandins enhance gastric emptying in monkeys (143). Whether this has any connection with aspirin induced gastric mucosal lesions is unknown. Finally, chronic ingestion of fiber in the form of pectin but not in the form of cellulose prolonged gastric emptying time approximately two-fold (144). The mechanism of this effect is unknown.

MEASURING GASTRIC MOTOR FUNCTION

The greatest roadblock to a better understanding of normal and aberrant gastric motor function has been the lack of adequate experimental and clinical techniques to measure motor function. This section will discuss those methods which are applicable to the study of gastric motor function in human beings. In general, these fall into five categories: 1) measurement of intraluminal pressure, 2) measurement of gastric electrical activity, 3) radiological methods, 4) intubation methods and 5) scintigraphic methods. Each method has drawbacks and limitations and none is able to give a complete picture of gastric motor activity and its consequences. Few of these methods have proven clinical usefulness.

Measurements of Intraluminal Pressure.
Intragastric balloons, perfused catheters and intragastric miniature transducers have all been used to measure the force of gastric contractions (83). While such measurements produce records that can be classified by the magnitude of the pressures generated, knowledge of these patterns cannot be usefully extrapolated to a description of gastric motor function (such as emptying) because of the complex relationship between motor activity and motor function. In spite of this, these methods are still some-times used in research settings to assess gastric motor function (particularly during the interdigestive interval) and the effects of drug therapy, where muscle activity may be grossly altered. Another use for balloon pressure measurements is the study of gastric accomodation (46) for which a large, flaccid balloon is placed in the stomach and then inflated with varying volumes of water or air. Clinically, such studies are used in only a few referral centers to explore pathophysiology in patients with chronic, severe motor disorders.

Measurement of Gastric Electrical Activity. In vivo measurement of human gastric electrical activity has been quite limited. Suction electrodes are available to record muscle potentials directly in intact subjects (83), but these have been used infrequently. Occasionally, serosal electrodes have been implanted surgically for long term monitoring of patients (145). Electrical activity can also be measured indirectly by the technique of electrogastrography (146). In this technique, electrical potentials on the skin are recorded and signals representing electrical slow wave and action potentials can be extracted. Interest in electrogastrography, a method first utilized in the early part of this century, has been revived with the development of newer computer technology. Since abnormalities in electrical activity may underlie gastric retention in some individuals, this method may prove to be a helpful, non-invasive diagnostic test. However, the clinical usefulness of this test is yet to be defined.

Radiological Methods. Much of our current understanding of patterns of gastric motor activity dates back to the fluoroscopic observations of Cannon (43) at the turn of the century. However, quantitative assessment of gastric emptying with barium contrast radiography has been technically difficult: it is virtually impossible to know when 5, 10 or even 50% of the barium has left the stomach and only the complete emptying time can be measured reproduceably (147). Moreover, the relationship of the emptying of barium to the emptying of food is uncertain and barium mixed with food in vitro may separate out in vivo. In spite of these problems, the conventional barium contrast examination remains the most useful clinical test of gastric motor function. This is largely

because of its widespread availability and the fact that extremely fast or slow emptying can usually be identified. For most clinical purposes, a more quantitative or more sensitive test is not needed since, at present, therapeutic decisions for most disorders of gastric emptying depend more on the patient's history rather than on the accurate measurement of the rate of emptying.

Drs. Mark Feldman and Herbert Smith at the Dallas Veterans Administration Medical Center have recently described a radiographic test using radiopaque markers and fluoroscopic equipment available at virtually every hospital (148). In this test, 10 small pieces of radiopaque tubing are swallowed along with a meal of two donuts and 7-UP. The evacuation of the radiopaque markers is followed fluoroscopically. Since they are indigestible solids, the markers are retained in the stomach until the digestible components of the meal are emptied and interdigestive motor activity resumes. Studies in normal individuals indicate that all 10 radiopaque markers should be emptied from the stomach within 6 hours. Studies in diabetics (a group with a high incidence of gastric motor dysfunction) show a significant delay in the emptying of the markers (Figure 29). This test promises to be a sensitive clinical test of disturbances in gastric emptying, particularly those involving the interdigestive migrating motor complex which plays an important role in the emptying of indigestible solids from the stomach.

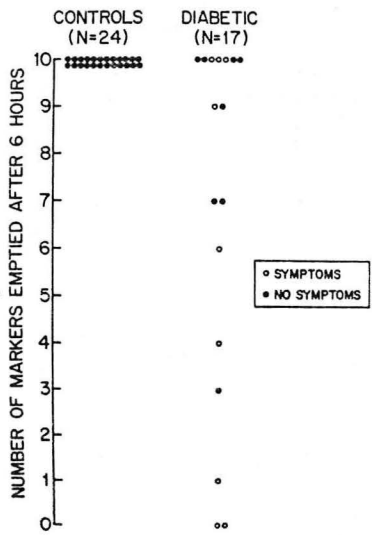
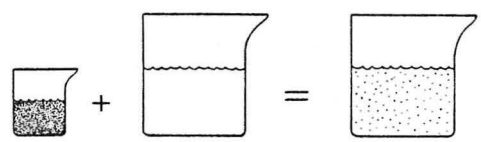


FIGURE 29. Emptying of radiopaque markers from the stomachs of normal controls and symptomatic and asymptomatic diabetic patients. Most of the diabetics failed to empty all of the markers from their stomachs after 6 hours. All of the controls emptied all 10 markers within this time span.

Intubation Methods. Measurement of gastric volume by aspiration or by indicator dilution has been widely used to quantitate gastric emptying in research studies. Clinical applications have been limited. In its simplest form, a known volume of a liquid test meal is infused into the stomach and then aspirated some time later. The difference between infused and recovered volumes is supposed to represent the volume emptied. In reality, this is not the case since gastric secretion adds an unquantified volume to gastric contents and recovery by aspiration is seldom complete. Nonetheless, such a test (saline load test [149]) has been used clinically to predict the course of patients with gastric outlet obstruction. Because of inaccuracies and lack of specificity, this test should no longer be used clinically. Addition of a nonabsorbable marker (150) to a test meal allows correction for gastric secretion. Such modified tests, using aspiration at various times after infusion of the test meal on separate test days, have formed the basis of our understanding of the regulation of emptying (86).

Another intubation method for assessing emptying is the double sampling indicator dilution method first developed by Hildes & Dunlop (151) in 1951 and rediscovered by George (152) in 1968. In this method, a concentrated aliquot of nonabsorbable marker is added to the stomach. By measuring the concentration of marker in gastric contents before and after addition of the concentrated aliquot, the gastric volume can be calculated (Figure 30). The only assumptions are that mixing of the marker with the meal is complete and that the fraction emptied during the procedure is negligible. This method allows repeated volume estimates with the same meal on the same test day (unlike aspiration which removes the entire meal from the stomach), but certain modifications (153) have been suggested for maximum accuracy with multiple estimations. By adding an additional marker to the meal, the volume of secretions, the amount of meal remaining in the stomach and the actual volume of gastric contents emptied can also be estimated (96).

MEASUREMENT OF VOLUME
BY INDICATOR DILUTION



$$V_A C_A + V_1 C_1 = (V_A + V_1) C_2$$

$$V_1 = V_A \frac{(C_A - C_2)}{(C_2 - C_1)}$$

FIGURE 30. Measurement of volume by indicator dilution. A concentrated volume of a non-absorbable marker (small beaker) of known volume (V_A) and concentration (C_A) is mixed with an unknown volume of fluid (V_1) containing a measurable concentration of marker (C_1) (large beaker) and the concentration of marker in the resulting fluid is measured. Since the total mass of non-absorbable marker is assumed not to change, the equations can be solved for the unknown volume.

Aspiration or indicator dilution are suitable only for liquid meals. Estimation of emptying of a mixed liquid-solid meal by intubation methods can be done by either of two techniques. The first technique is to estimate buffer content by intragastric titration (154): the amount of base needed to bring gastric contents to a preselected pH level depends on the amount of buffering material in the stomach, and presumably, the mass of gastric contents. The other technique involves ingestion of a meal including a non-absorbable marker and duodenal perfusion with a second marker (155). By measuring marker concentrations distally and by using appropriate formulae, it is possible to calculate gastric emptying and secretion. Recent studies (156,157) make it clear, however, that intubation itself may introduce artifacts in the measurement of gastric motor function.

Scintigraphic Methods. The development of gamma cameras and sophisticated computers in the last decade now allows quantitative estimates of gastric emptying by scintigraphic methods (158,159). In these studies, a radioisotope is used to label a specific fraction of the meal. Soluble liquid markers, such as ^{113m} indium DTPA chelate and ^{51}Cr sodium chromate (160), and solid food markers, such as ^{51}Cr sodium chromate cooked into eggs (161), ^{99m} technetium-sulfur colloid absorbed on filter paper (162) or incorporated into chicken liver (161), ^{123}iodine-labelled noodles (79), and ^{131}iodine-labelled cellulose (163) have been employed with varying success. The marked food is mixed with the meal and ingested. A gamma camera is then used to measure the amount of isotope remaining in the region of the stomach (Figure 31) and repeated observations allow the development of a curve of percent of original activity remaining in the stomach area versus time. This method does not require intubation, exposes

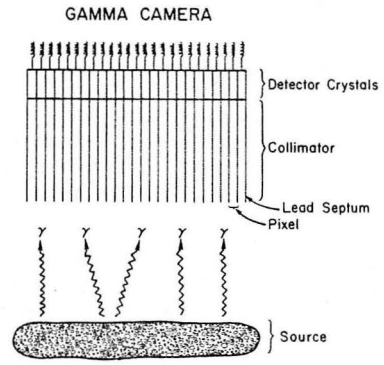


FIGURE 31. A gamma camera detects and quantitates radiation of a given energy emitted by a source. Collimation with lead septa insures that the detector is measuring the flux of radiation from a defined area and not from adjacent regions. An array of detector crystals defines the picture areas or pixels that are imaged and supplies an electrical output to a computer for analysis.

the patient or subject to relatively low levels of radiation, can be used with ordinary mixed meals, can assess two or more meal components simultaneously, and appears to be reproducible. However, technical problems with the stability of isotope labelling (161), measurement of isotope counts (79), the type of equipment used (164,165), and patient positioning (164-166) must all be considered. Other variables such as the composition of the test meal (79), and the construction and interpretation of the emptying curve (167-169) also make comparisons from one study to another difficult. Moreover, as usually performed, scintigraphic studies do not quantitate the volume of gastric secretion or the actual volume in the stomach, and extrapolation to the actual amount of food emptied from the stomach must be tempered by the realization that only one or two components of the meal were labelled.

In spite of these problems, these studies are increasingly available at hospitals throughout the country; however, clinicians should approach them with caution. Technical factors should be standardized at a given institution. A series of normal individuals should be tested with this standardized procedure since published controls may not be relevant. Finally, the test should be interpreted with care. The clinical significance of minor or even moderate abnormalities in gastric emptying is uncertain and clinical correlation is sketchy at best at present.

Other Methods. Real-time ultrasound (170,171) has been reported as a way of measuring and visualizing gastric movements but further studies are needed. Another novel method of quantifying emptying is measurement of the secondary magnetic field created by ingested iron granules during exposure to an imposed external magnetic field (172). This method can quantify emptying while avoiding the ionizing radiation used in scintigraphy. Again, further studies of this application are needed to assess its value.

GASTRIC MOTOR DISORDERS

Many conditions are associated with abnormalities of gastric motor function. For many of these, the gastric motor disturbance is of little consequence. For some, the gastric motor dysfunction produces symptoms that warrant attention. In others, alterations in gastric motor function produce severe or chronic disability.

In general, these disorders remain poorly defined, largely because of difficulties in fitting these disorders into a rational pathophysiologic framework but also because of conflicting results generated by the wide variety of techniques and test meals used in investigations of these disorders. Renewed interest in gastric motor disorders may shed new light on these problems and holds the hope of improved diagnosis and treatment.

Clinical Spectrum of Gastric Motor Disorders.

Investigations of several gastrointestinal disorders have revealed alterations from the normal pattern of gastric emptying. In some conditions, these alterations are mild, have not been confirmed by all investigators, and would seem to have little to do with the pathogenesis or symptoms produced by the underlying disorder. Examples of such alterations are the rapid gastric

emptying reported in duodenal ulcer disease (154,173,174), Zollinger-Ellison Syndrome (175) and obesity (176) and the slower than normal emptying reported in some cases of atrophic gastritis or achlorhydria (83,177), gastric ulcer (178) and anorexia nervosa (179). Of somewhat greater potential clinical importance are impaired accommodation and accelerated gastric emptying with Chagas Disease (180), rapid emptying with malabsorption syndromes including pancreatic insufficiency (83) and the slow emptying noted with acute hyperglycemia (181) and high-calorie parenteral nutrition (182).

In other disorders, abnormal gastric motor function probably contributes to the production of symptoms in some individuals. Examples of these conditions are viral gastroenteritis and reflux esophagitis. Viral gastroenteritis is usually accompanied by nausea and vomiting which may, in part, be due to delayed emptying (183). In some instances, an illness resembling viral gastroenteritis appears to predate the onset of more chronic disturbances of gastric emptying (184). Reflux esophagitis patients also have had gastric motor function assessed because of the thought that the volume of gastric contents might be a determinant of gastroesophageal reflux, and specifically that slow emptying might promote reflux. Marginal slowing of gastric emptying (185-188) and abnormal antral motility (189) have been reported in some patients. It has been suggested that therapy with stimulants of gastric emptying, such as metoclopramide, might decrease symptoms by reducing the amount of gastric contents available to reflux into the esophagus. However, it is unclear to what extent symptomatic improvement with metoclopramide results from speeding gastric emptying rather than simultaneous changes in lower esophageal sphincter pressure or esophageal mechanics.

In still other patients, abnormalities in gastric motor function produce disabling symptoms and poor nutrition. The settings in which this degree of symptomatic gastric motor dysfunction can be found are listed in Table 3.

TABLE 3. CONDITIONS PRODUCING SYMPTOMATIC GASTRIC MOTOR DYSFUNCTION

ACUTE	CHRONIC	EITHER ACUTE OR CHRONIC
Abdominal Pain/Trauma/ Inflammation	Diabetes mellitus	Mechanical Obstruction
Acute Infections/Gastro-enteritis	Gastric Surgery	Drugs/Toxins:
Acute Metabolic Disorders:	Vagotomy	Morphine
Acidosis, Hypokalemia,	Dysautonomia	Anticholinergics
Hyper- or hypocalcemia,	Chagas Disease	Psychotropic Drugs
Hepatic Coma,	Brain Tumors	Pregnancy
Myxedema	Smooth Muscle Myopathies	Tabes dorsalis
Immobilization	Scleroderma, Dermato-myositis	
	Familial Visceral Myopathy	
	Myotonic Dystrophy	
	? Progressive Muscular Dystrophy (Duchenne)	
	Infiltrative Diseases	
	Carcinoma	
	Amyloidosis	
	Idiopathic Disorders:	
	Pseudo-obstruction	
	Antral Tachygastria	

Pathophysiology of Some Selected Entities Producing Symptomatic Gastric Motor Dysfunction

Diabetes Mellitus. Although the association of nausea, vomiting and x-ray evidence of gastric retention has long been recognized in patients with diabetic autonomic neuropathy, it is only recently that milder degrees of gastric motor dysfunction have been identified in diabetic patients without nausea or vomiting (190). The motor abnormalities of diabetic gastroparesis, as the symptomatic condition is known, involve both the proximal and distal stomach. Both fundic (191) and antral (191,192) contractions were reduced during the interdigestive period when measured with balloon or luminal manometry in symptomatic patients. Typical bursts of interdigestive motor activity did not occur in the stomach (191,192) although they were preserved in the intestine (191). In another study, the diabetic stomach was unable to discriminate normally between the solid and liquid components of a mixed meal, suggesting that meal-related antral function is also disturbed (190). This conclusion is also supported by the finding that the emptying of solids is affected more than the emptying of liquids in most of these patients (193).

Studies of the pathogenesis of diabetic gastroparesis have concentrated on neural dysfunction, because coexisting symptoms of autonomic neuropathy are often so dramatic. Patients with longstanding diabetes with or without vomiting have reduced vagally-mediated acid secretion, suggesting that they have a vagal neuropathy (194). Moreover, diabetic patients with gastrointestinal complications often have delayed esophageal transit, again suggesting vagal dysfunction (195). However, clearcut evidence of abnormal vagal gastric function in diabetics has not yet been produced. Decreased vagal-cholinergic activity probably contributes to diabetic gastroparesis because administration of the cholinergic drug, bethanechol, reversed abnormal antral motor activity in two studies (191, 192) in patients with this disorder. However, other factors probably also contribute to symptomatic relapses in these patients.

Vagotomy. Gastroparesis may also occur after vagotomy either transiently in the early post-operative period or chronically. In some respects it is similar to diabetic gastroparesis since interdigestive motor bursts are absent and basal motor activity is reduced (191). However, unlike diabetic gastroparesis, interdigestive motor bursts can be fully restored by metoclopramide (191). It has been suggested on this basis (191) that the neural defect in post-vagotomy gastroparesis is less extensive than the defect in diabetic gastroparesis but this remains to be established.

Like diabetic gastroparesis, patients with post-vagotomy gastroparesis generally have abnormally slow emptying of solids but may have normal or even abnormally rapid emptying of liquids. This is because vagotomy abolishes gastric accommodation causing intragastric pressure to be greater for any given volume of liquid consumed. Because the emptying of liquids is proportional to intragastric pressure and, to a lesser extent, because pyloric resistance is often concomitantly eliminated or reduced (by antrectomy or by pyloroplasty), liquid emptying is accelerated by vagotomy. This may actually produce symptoms of dumping syndrome (see below) at the same time that the patient has symptoms produced by the slow emptying of solids.

Dumping Syndrome. Operations which result in creation of a gastroenterostomy or otherwise alter gastroduodenal anatomy (e.g., vagotomy and

pyloroplasty) may lead to rapid gastric emptying and a group of disabling symptoms known collectively as the dumping syndrome (196). These symptoms occur early, within 15-30 minutes of the start of a meal or may occur later, approximately 90-120 minutes after the meal. The early symptoms include anxiety, weakness, dizziness, tachycardia with a pounding pulse, sweating, flushing, abdominal cramps and diarrhea. Late symptoms are those of hypoglycemia: weakness, sweating, tachycardia and sometimes a decreased level of consciousness. Patients with either symptom pattern, but especially those with the early symptom complex, may reduce food intake to avoid symptoms and therefore lose weight.

The pathophysiology of dumping is not yet fully understood. Exposure of the intestine to hypertonic chyme can reproduce symptoms in patients or induce similar symptoms in normal individuals. For a long time, it was thought that the symptoms were due only to rapid fluid shifts from plasma to intestinal lumen as a result of osmotic gradients. However, hypovolemia alone could not explain all of the vasomotor manifestations of the early dumping syndrome and other mechanisms were sought. In one experiment (197), the vasomotor changes of dumping could be induced in normal dogs by transfusion of plasma from symptomatic animals, suggesting that a humoral mediator was involved. Since that time, several mediators for dumping have been suggested, including serotonin, bradykinin, prostaglandins and various peptides (196). The identity of the mediator(s) of early dumping syndrome remains unknown. The late dumping syndrome is thought to be due to reactive hypoglycemia as a result of rapid gastric emptying and excessive release of insulin but, in one study, postcibal symptoms could not be correlated with serum glucose (198).

Idiopathic Gastroparesis. This group of disorders is of great interest because electrophysiological studies now allow better definition of pathophysiology in some of these patients. One of these idiopathic disorders is antral tachygastria (199,200). In this condition, an aberrant pacemaker in the antrum cycles at a rapid rate, some 3 to 4 times faster than the usual pacemaker area in the corpus. Slow waves are transmitted proximally into the corpus as well as distally into the terminal antrum (Figure 32). Such aberrantly directed electrical activity might be expected to disrupt antral motor function and prevent peristalsis in and of itself, but muscle of the tachygastric stomach has an additional abnormality. When smooth muscle strips from affected persons are examined with intracellular electrodes in vitro, the usual antral plateau potential is markedly decreased or absent and cannot be increased by stimulants such as acetylcholine or gastrin (199). This second abnormality results in little or no spontaneous mechanical activity in the distal stomach, since the transmembrane potential does not remain above the mechanical threshold.

The electrical activity of antral muscle from one patient with tachygastria could be normalized in vitro by incubating the muscle tissue with the prostaglandin inhibitor, indomethacin (201). With indomethacin, a normal frequency of action potentials, a normal plateau potential, and normal reactivity to acetylcholine and gastrin all returned, suggesting that these abnormalities were due to elevated levels of prostaglandins. Addition of PGE_2, a prostaglandin which has been reported to increase the frequency of action potentials and decrease the plateau potential in canine antrum, caused electrical activity to revert to its abnormal state (201).

Application of similar techniques to other patients with "functional" symptoms, such as dyspepsia (200,202,203), may uncover additional patients with

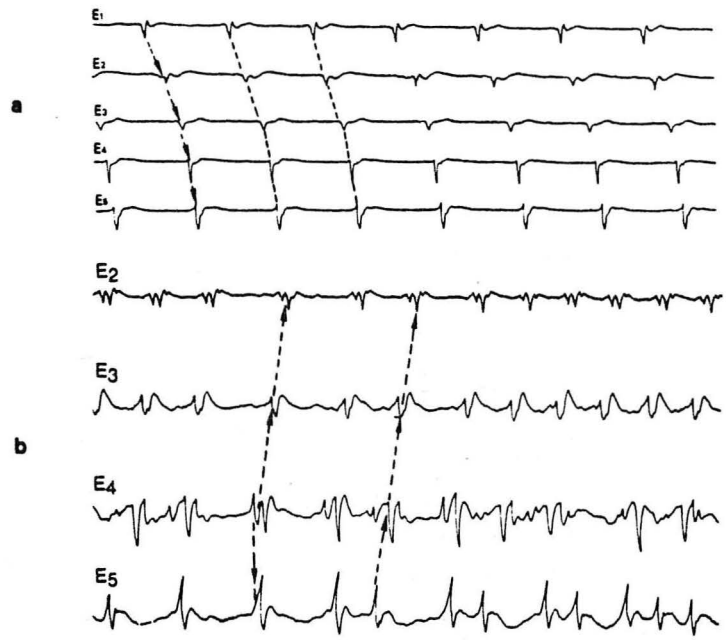


FIGURE 32. In vitro myoelectric recording from antral muscle from a duodenal ulcer patient (a) and a patient with antral tachygastria (b). Electrodes were placed in an array from the proximal to distal parts of the muscle strip. In the duodenal ulcer patient, electrical activity propagates from proximal to distal recording sites at a regular rate. In the patient with tachygastria, electrical activity propagates from distal to proximal sites and occurs at an irregular rate. (From Reference 203).

idiopathic gastric motor disorders. However, a word of caution is in order. Some patients (studied postoperatively with surgically placed gastric electrodes) had electrical arrhythmias but were asymptomatic (145). Thus the clinical significance of gastric dysrhythmias remains undefined at present.

APPROACH TO PATIENTS WITH SUSPECTED GASTRIC MOTOR DISORDERS

A stepwise approach to patients with suspected gastric motor disorders is outlined in Figure 33. The physician must first recognize the possibility that the patient has motor dysfunction of the stomach. An initial evaluation is then done to exclude mechanical obstruction and other conditions as the cause of these symptoms. Next, if the clinical picture is clear, a diagnosis may be ren-

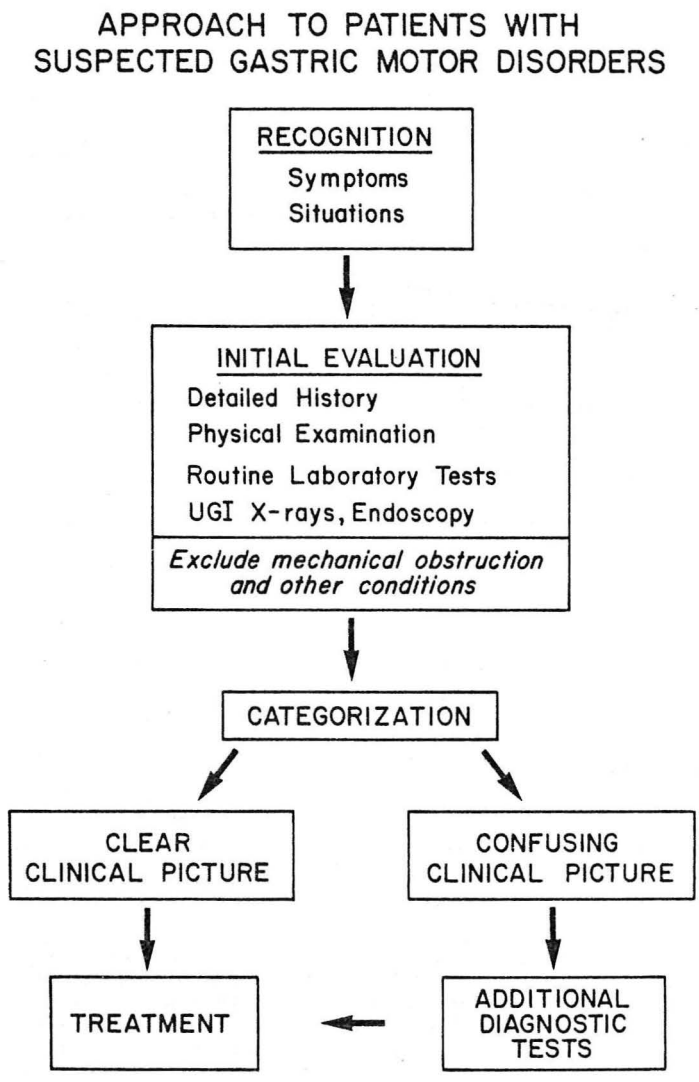

APPROACH TO PATIENTS WITH
SUSPECTED GASTRIC MOTOR DISORDERS
RECOGNITION
Symptoms
Situations
INITIAL EVALUATION
Detailed History
Physical Examination
Routine Laboratory Tests
UGI X-rays, Endoscopy
Exclude mechanical obstruction and other conditions
CATEGORIZATION
CLEAR CLINICAL PICTURE
CONFUSING CLINICAL PICTURE
TREATMENT
ADDITIONAL DIAGNOSTIC TESTS

FIGURE 33.

dered and treatment instituted or, if the clinical picture remains confusing, further diagnostic tests can be ordered. Each of the steps will now be discussed in some detail.

Recognition of Gastric Motor Dysfunction

Symptoms of disordered gastric motor function are listed in Table 4. These symptoms may be due to failure of the stomach to accommodate ingested food (impaired storage function) or may be due to either precipitous or tardy gastric emptying (impaired emptying function). When present, any of these symptoms should suggest the possibility that gastric motor dysfunction is present. However, these symptoms are protean and non-specific for gastric motor dysfunction, making recognition of affected individuals difficult.

TABLE 4. SYMPTOMS OF GASTRIC MOTOR DYSFUNCTION

SUGGESTING SLOW EMPTYING	SUGGESTING RAPID EMPTYING
Nausea	Anxiety*
Vomiting	Weakness*
Bloating, Fullness	Dizziness*
Early Satiety	Tachycardia*
Dyspepsia	Sweating*
Heartburn	Flushing*
Anorexia	Decreased consciousness
Weight loss	Food avoidance

* Soon after ingestion of a meal

Gastric motor dysfunction should be suspected in particular when the symptoms of disordered gastric motor function listed in Table 4 are present in an individual with any of a variety of other conditions known to produce symptomatic gastric motor dysfunction, such as diabetes mellitus, gastric surgery or vagotomy. A list of these conditions is provided in Table 3.

Initial Evaluation of Patients with Suspected Gastric Motor Disorders

History. Once gastric motor dysfunction is suspected, it is vital to obtain a detailed history, because the history is the most useful criterion of severity

and the best way of following the patient and judging the results of therapy. In this regard, the physician should attempt to define the frequency of symptoms, the types of meals that induce symptoms, any weight loss that has occurred, the disability produced by these symptoms, and the patient's perception of the problem. An informal psychosocial assessment can also be helpful in dealing with these patients. Possible historical findings and their implications are listed in Table 5.

TABLE 5. HISTORICAL FINDINGS AND THEIR IMPLICATIONS IN PATIENTS WITH SUSPECTED GASTRIC MOTOR DYSFUNCTION

FINDING	IMPLICATION
TIMING OF SYMPTOMS	
Minutes After Meals	Psychoneurotic Vomiting, Bulimic Vomiting, Vomiting due to Channel Ulcer, Early Dumping Syndrome
Hours After Meals	Mechanical Obstruction, Gastroparesis
Before Breakfast	Pregnancy, Uremia, Alcoholism, Increased Intracranial Pressure, After Gastric Surgery
DURATION OF SYMPTOMS	
Hours - Days	Acute Infections, Drugs, Toxins/ Poisons, Acute Inflammatory Conditions, Pregnancy
Weeks - Months	Mechanical Obstruction, Gastroparesis, Brain Tumors, Psychogenic Vomiting
QUALITY OF VOMITUS	
Partially-Digested Old Food	Gastroparesis, Obstruction
Undigested Food	Esophageal Obstruction or Diverticulum
Bile Present	Gastric Outlet Patent
Feculent Odor	Gastroparesis with Stasis, Intestinal Obstruction, Gastro-colonic fistula
Blood Present	Cancer or Inflammation
AMENORRHEA	Pregnancy
HEADACHE	Brain Tumor
PREVIOUS SURGERY	Post-vagotomy Gastroparesis, Dumping Syndrome, Other Postgastrectomy Syndromes, Mechanical Obstruction

Physical Examination. Patients with suspected gastric motor disorders should be checked for objective evidence of weight loss and have a careful abdominal examination. Note should be made of the presence of a succussion splash. If this finding is present more than 4 or 5 hours after a meal, it supports the diagnosis of gastric retention (delayed gastric emptying) although it provides no evidence as to the etiology of this condition.

Routine Laboratory Tests. Standard blood counts and chemistries may provide supportive evidence for impaired nutrition or electrolyte imbalance in these patients. Blood glucose levels should be checked for evidence of glucose intolerance and diabetes mellitus in patients with slow gastric emptying, and for evidence of hyperglycemia and reactive hypoglycemia in patients with suspected dumping syndrome even though symptoms may not always correlate with blood glucose concentrations (198). In some cases, a formal glucose tolerance test (with blood collection for 6 hours) in useful. In women of childbearing age, a pregnancy test is vital before proceeding with radiological tests.

UGI X-rays, Endoscopy. Some patients need no further diagnostic tests at this point. These include patients previously subjected to gastric surgery who have clear-cut evidence for dumping syndrome and pregnant women with morning sickness. These individuals can be treated with dietary and other advice as a therapeutic trial.

Most other patients, especially those with symptoms compatible with delayed gastric emptying need to have mechanical obstruction and other conditions excluded. This is important because one would not like to overlook a surgically-correctable cause for the patient's symptoms. Usually, this can be done best by means of a carefully performed barium contrast study (UGI series). Although barium is a non-nutritive liquid and it is not emptied by the same mechanism as food, valuable information can be gained from this study. The diagnosis of gastric retention is supported by poor emptying of barium from the stomach, gastric dilatation and the presence of retained food or a gastric bezoar (Figure 34). Mechanical obstruction may produce the same picture and endoscopic inspection of the gastric outlet is often necessary to exclude obstruction. On the other hand, if barium passes out of the stomach freely, mechanical obstruction is not present. It should be noted, however, that such a result does not indicate that there is no disease present, just that there is not mechanical obstruction. A considerable defect in the emptying of solids or of nutritive liquids may still be present. The barium contrast study may also indicate the presence of other conditions, such as carcinoma or peptic ulcer disease.

Categorization of Patients and Additional Diagnostic Tests

At this point in their investigation, patients will fall into two categories: those presenting with a clear clinical picture and those in whom the clinical picture is still confusing. An example of the first category is a patient with longstanding diabetes mellitus presenting with nausea and vomiting of old food, a dilated stomach with residual food present on UGI x-rays and poor emptying of barium from the stomach. Such a patient might undergo endoscopy to be certain that there was no gastric outlet obstruction but further investigation would not be indicated. A diagnosis of diabetic gastroparesis could be made and therapy instituted. On the other hand, another patient might be just

FIGURE 34. Radiograph of a patient with gastric motor dysfunction showing retained food after a 12-hour fast.

as symptomatic as the diabetic patient just mentioned but have no specific history and no abnormalities on UGI x-ray. Diagnosis in such a patient requires further study.

TABLE 6.

ADDITIONAL DIAGNOSTIC TESTS THAT CAN BE USED IN SELECTED PATIENTS

1. To identify impaired gastric emptying:
a. Intubation Emptying Tests
b. Scintigraphic Emptying Tests
c. Radiographic Emptying Test
2. To examine pathophysiology:*
a. Gastric Manometric Studies
b. Electrogastrography

* Available in only a few referral centers.

Additional diagnostic tests that can be used in selected patients are listed in Table 6. These tests are basically designed to answer two questions: a) is gastric emptying impaired, and b) what is the pathophysiology of the problem? Unfortunately, our present level of knowledge does not allow any other use of these tests, i.e., to tailor therapy, although there is beginning to be an attempt to do so (204). Still, these tests are sometimes helpful clinically, if for no other reason than that they provide additional evidence for organic dysfunction in some patients in whom other evidence is inconclusive. Sophisticated diagnostic tests are also highlighting the limitations of diagnosis by history alone, particularly in postoperative patients (205). At present, these advanced diagnostic tests are not widely available throughout the United States. Even scintigraphy which has been heralded as the future standard clinical method for assessing gastric motor function is not available as a standarized, routine procedure in most hospitals. Tests examining the pathophysiology of patients with gastric motor disorders are available at only a few referral centers in the United States but may help to classify these disorders (200,202,206) and assess treatment modalities (205,206).

Treatment of Patients with Gastric Motor Disorders

Table 7 summarizes an approach to the treatment of patients with gastric motor dysfunction. If an underlying disease process has been identified, such as diabetes mellitus or any of the acute processes listed in Table 3, it should be treated in the hope that the gastric motor problem will resolve. This is particularly likely for acute gastric retention, but may also be true to some extent for diabetic gastroparesis. There are several anecdotal reports of spontaneous improvement in gastric motor function in diabetics with gastroparesis

TABLE 12. TREATMENT OF GASTRIC MOTOR DYSFUNCTION

1. Treat underlying disease process, if possible.	
2. Dietary advice and nutritional support	
a. Malnutrition:	enteral supplements or parenteral alimentation
b. Rapid Emptying:	dry foods; avoid hypertonic, glucose-rich beverages; small, frequent feedings
c. Slow Emptying:	increase nutritive liquids; avoid hypertonic beverages; decrease undigestible material (fiber-rich foods)
3. Drug Therapy	
a. Bethanechol (Urecholine)	
b. Metoclopramide (Reglan)	
c. Traditional antemetic drugs	
d. Investigational drugs	
4. Surgery	

with strict control of blood sugar concentrations (207). A period of nasogastric suction may also be useful in patients with slow gastric emptying although the efficacy of this is not proven. One patient with chronic gastric stasis and vomiting was helped with behavioral therapy (208), but more studies of this modality are needed.

Diet. Dietary advice and nutritional support are also important. Many patients with gastric motor disorders will have lost weight and will be catabolic. Efforts should be made to increase nutrient intake via the oral route (liquid feedings are sometimes better tolerated than regular foods) or, if necessary, by enteric tube feeding or by parenteral alimentation. Reestablishment of adequate nutrient intake removes much of the urgency about correcting gastric motor dysfunction and can allow an orderly evaluation to take place.

In individuals taking food by mouth who have gastric motor dysfunction, adjustment of the type of food ingested may ameliorate symptoms. Patients with the rapid gastric emptying of dumping syndrome should be advised to eat more dry foods and to avoid hypertonic, glucose-rich beverages, since precipitous emptying of hypertonic liquids is thought to be responsible for the production of symptoms in these patients. Small, frequent feedings are also advised in patients with rapid emptying in an attempt to smooth out the caloric load presented to the intestine (196).

In patients with slow gastric emptying, it is sensible to increase nutritive liquids in the diet since emptying of liquids may be less affected than the emptying of solids. It is important to use liquids that are isotonic, however, since hypertonic liquids will further slow emptying. It also seems sensible to reduce the load of undigestible material in these patients, since interdigestive motor activity which clears the stomach of such material is often absent in these patients.

Drug Therapy. While it makes sense to treat patients with rapid gastric emptying with agents that slow emptying, such as anticholinergics or opiates, clinical results with these agents have been disappointing. On the other hand, patients with slow gastric emptying often benefit from judicious drug therapy. Two agents are often used: bethanechol (Urecholine) and metoclopramide (Reglan).

Bethanechol is a cholinergic agonist drug that stimulates muscarinic receptors on smooth muscle cells (209). This results in more powerful contraction and consequently an increase in tone in the proximal stomach and an increase in the force developed by peristaltic waves in the distal stomach. The net effect of bethanechol in at least some patients with gastric retention is to improve gastric motor function. Bethanechol should be started in doses of 5-10 mg before meals. Often high doses of bethanechol have to be used (up to 40-50 mg before meals) but side effects, such as excessive salivation and abdominal cramping or diarrhea, sometimes limit their use. Bethanechol has not been approved by the Food and Drug Administration for this indication.

Metoclopramide also has cholinergic activity but this seems to be more limited to the proximal gastrointestinal tract than that of bethanechol. Metoclopramide also has other actions which make it an attractive drug to use in patients with delayed gastric emptying (210). For one thing, metoclopramide has anti-dopaminergic properties in the stomach. Since dopamine is thought to be a mediator of gastric relaxation (50), metoclopromide inhibits this relaxation, increasing intragastric pressure and favoring gastric emptying of liquids. In normal subjects, metoclopramide accelerates the emptying of liquids only slightly (211) and has no effect on the emptying of a solid meal (212,213). In contrast, both liquid and solid emptying are accelerated significantly in patients with impaired gastric emptying (211-215). This difference between normal individuals and patients with delayed gastric emptying is unexplained. However, the improvement of gastric emptying with metoclopramide in patients has been attributed to both sensitization of gastric smooth muscle to acetylcholine (216) and antidopaminergic effects (135). It is of interest in light of this double mechanism of action that metoclopramide proved to be superior to bethanechol (muscarinic effects only) in speeding emptying in one trial (215).

Metoclopramide also has central antidopaminergic actions which appear to mediate a direct antemetic action in the medulla. In comparison to traditional

antemetic drugs, metoclopramide has a greater therapeutic index and is more effective in suppressing nausea and vomiting (217). This central antemetic action may be responsible for much of the symptomatic improvement noted in controlled trials in patients with diabetic gastroparesis since symptoms improved with metoclopramide therapy much more than objective tests of gastric emptying improved (218).

The central effects of metoclopramide also are responsible for its most bothersome central nervous system side-effects, such as nervousness, somnolence, dystonic reactions and akathisia (motor restlessness). These side effects occur in 10-20% of patients given this drug. Central anti-dopaminergic action also probably accounts for prolactin release seen with metoclopramide, but the clinical significance of this effect is uncertain (219).

All in all, metoclopramide is the drug of first choice in the treatment of non-obstructive gastric retention. It should be given in doses of 10-20 mg before meals and at bedtime. If gastric emptying is so poor that the tablets will not be emptied from the stomach, metoclopramide may have to be given either as an oral suspension or parenterally for a while. It may take up to several weeks to achieve optimal clinical results and any therapeutic trial of metoclopramide should be continued for at least one month unless side effects supervene.

Some patients respond to traditional antemetic drugs, such as prochlorperazine (Compazine) or trimethobenzamide (Tigan). Since the therapeutic index for these antemetic drugs is less than that for metoclopramide, and since some of these drugs have anticholinergic properties which might impair gastric function, these agents should be second line drugs in treating nausea and vomiting in patients with gastric motor disorders.

Two additional drugs are under investigation for use in patients with slow gastric emptying. Domperidone is a peripheral dopamine antagonist like metoclopramide but apparently has no central effects (220-223). It is available for investigational use in this country and may be useful in patients who cannot tolerate metoclopramide because of its central nervous system side-effects. Preliminary studies indicate that it may be useful in patients with functional dyspepsia, a condition that may be due to gastric motor dysfunction (224). The other agent being investigated for use in patients with gastric emptying disorders is lidamidine hydrochloride (225). This agent is an adrenergic agonist and appears to improve symptoms in some patients with idiopathic motor disorders producing dyspepsia. This agent has not yet been released for general clinical use.

Surgery. Operative therapy is usually needed in cases of mechanical obstruction. Indications for surgery in non-obstructive gastric retention or in cases of rapid gastric emptying are less clear and the results of surgery in such cases are unpredictable. Because of this, surgery should be a therapy of last resort in most individuals with disorders of gastric emptying. However, there are two situations in which surgery may be useful and may have to be considered sooner.

The first is severe dumping syndrome unrelieved by dietary manipulation. These patients often have Billroth II gastrojejunostomies, and sometimes operative reconstruction to create a gastroduodenostomy (Billroth I) or analogous

anastomosis mitigates the patient's symptoms. Recent work indicates that Roux-en-Y reconstruction or jejunal interposition significantly retards emptying (226,227), probably by altering the motility of the anastomosed small intestine (228). An intriguing but still experimental approach to this problem is the implantation of electrodes along the duodenum with retrograde pacing to attempt to retard gastric emptying by increasing duodenal resistance (229).

The second situation in which surgery may be useful is the patient who has an isolated, well-defined defect in antral function, such as antral tachygastria. In these individuals, antrectomy improves symptoms by removing the dysfunctional segment. It is essential that patients in whom surgery is considered to treat gastric motor dysfunction are thoroughly evaluated before recommending operative therapy to be certain that the preoperative diagnosis is correct (205).

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