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REVIEW ARTICLE

Postoperative Ileus

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Despite major advances in the understanding and treatment of disease in many areas of medicine, relatively few improvements have been made in the understanding of ileus. The most important advance in the therapy of functional or mechanical bowel obstruction was made over 50 years ago when Wangensteen (1) demonstrated that operative management of this problem could be delayed or replaced by nasogastric suction, greatly reducing mortality. Although improvements in supportive measures (such as intravenous fluid management and total parenteral nutrition) have helped management, no therapy to specifically reduce or eliminate the motility disorder underlying ileus has been forthcoming.

Precisely because we lack specific therapy, ileus remains an important clinical problem. Patients with this disorder accumulate gas and secretions leading to bloating, distension, emesis, and pain. Currently available therapies are not specific to postoperative ileus and are supportive in nature. These include nasogastric intubation and intravenous hydration. Patient discomfort is worsened by nasogastric tubes. Hospitalization costs increase as a result of the need for intravenous hydration, additional nursing care and laboratory tests, and increased hospital days. The expense due to ileus have been estimated at $1500 per patient or $750,000,000 annually (2).

Despite the importance of ileus, relatively little is known about the pathogenesis of this disorder. Since it may be induced by surgical manipulation, the process of harvesting tissue for study potentially activates the mechanisms responsible for ileus. Experiments require study of intact, unanesthetized animals and therefore limited amounts of information can be obtained utilizing current techniques. This review summarizes what is known about ileus and its treatment.

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HISTORY

The earliest studies of bowel motility focused on mechanisms for reduction and stimulation of intestinal contractions. Ileus, being a state of inhibited bowel function, naturally was the first pathologic state of bowel function to be explored.

When an animal's abdomen is opened, little spontaneous contractile activity is observed in the small bowel. Goltz noted in 1872 while observing exteriorized segments of bowel, division of the spinal cord at the level of the medulla greatly enhanced spontaneous contractions (3). This was the first demonstration of inhibitory spinal reflexes acting on the bowel. Less than 20 years later with the availability of radiologic means of assessing intestinal transit, reduction of motility following laparotomy was first described (4). At the turn of the century, Bayliss and Starling devised the enterograph, a device that enabled them to study the contractile activity of the small bowel in the intact, unanesthetized dog. Studying ileus, they found that division of the splanchnic nerves improved bowel contractility following laparotomy (5). Radiologic examination of cat gastric emptying demonstrated that cutaneous noxious stimuli delayed emptying, an effect partially reversed by splanchnicectomy (6, 7). Thus, early in this century the importance of inhibitory sympathetic reflexes mediating ileus was recognized. During the past 80 years a large number of studies have been published confirming these early findings (8–20).

With the inhibitory reflex's efferent limb clearly established, investigators searched for the afferent system. Many possibilities existed: peritoneal or cutaneous stimulation resulting in activation of reflex arcs, release of inhibitory humoral agents,

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inhibition of smooth muscle by inflammation, or muscle or nerve inhibition by anesthetic agents.

Arai demonstrated in 1922 that transit was markedly reduced after the experimental production of peritonitis in cats. Splanchnicectomized animals had rapid propulsion during the basal state with little inhibition following the induction of peritonitis (21). Other workers demonstrated splanchnic mediation of ileus not only after peritoneal irritation but also after cutaneous stimulation (22). Distension of the bowel was found to mediate inhibition of peristalsis (23), indicating that afferent fibers emanating from the bowel wall mediated the afferent limb of the inhibitory reflex. This was confirmed anatomically by Youmans (24), who hypothesized in 1952 that activation of the inhibitory efferent limb resulted in decreased splanchnic blood flow (25). Diminished splanchnic blood flow is a well-known consequence of adrenergic nerve stimulation, but its contribution to ileus remains unclear. Activation of cutaneous or visceral afferent fibers could mediate ileus through a common efferent pathway.

Early attempts at treating ileus focused on inhibition of splanchnic reflexes utilizing spinal anesthesia. Wagner first proposed the use of spinal anesthesia for the treatment of ileus in 1922 (26). Reduction of experimental ileus by spinal anesthesia confirmed that reflex pathways synapsing in the spinal cord are capable of inhibiting bowel motility (27–29), and early clinical trials reported this to be successful treatment of ileus (30, 31). More recent studies of this method have failed to demonstrate an improvement in colon motility after surgery (32). Other attempts at inhibiting this reflex have utilized splanchnic nerve anesthesia, a less practical solution than spinal anesthesia. Several reports indicated its efficacy in the treatment of ileus (3, 10, 33, 34).

PATHOPHYSIOLOGY

Nomenclature. There is no standard nomenclature regarding ileus. For purposes of this review ileus is defined as the functional inhibition of propulsive bowel activity, irrespective of pathogenetic mechanism. This is to be differentiated from motility disorders resulting from structural abnormalities, which is termed mechanical bowel obstruction. Ileus following surgery can be further classified into postoperative and paralytic ileus. We define postoperative ileus as the uncomplicated ileus occurring following surgery, resolving spontaneously within two to three days. The term postoperative paralytic ileus is modified from the definition by Catchpole (35) and is defined as that form of postoperative ileus gut lasting for more than three days following surgery.

Types of Ileus following Surgery. Regardless of the mechanism, transit of chyme distally is the ultimate indicator of bowel function. during ileus, no transit occurs. Presence of bowel sounds (36, 37) with subsequent passage of flatus or bowel movements indicates resumption of normal transit and marks the end of ileus. Uncomplicated ileus occurring after surgery, i.e., postoperative ileus, lasts only transiently in the small bowel (38–40) for 24–48 hr in the stomach and 48–72 hr in the colon (20, 41–45).

Occasionally, inhibition of bowel function is prolonged, lasting days to weeks and is described as postoperative paralytic ileus. Distinction between postoperative and postoperative paralytic ileus is important because they probably result from different pathogenetic mechanisms. Postoperative ileus most likely results from the temporary inhibition of extrinsic motility regulation and is more severe in the colon. Postoperative paralytic ileus affects all segments of the bowel and probably results from further inhibition of local, intrinsic contractile systems. Following laparotomy, ileus is more severe and is more likely to lead to postoperative paralytic ileus. Opening the peritoneum worsens ileus, although several animal and human studies have shown inhibition of bowel motility is independent of the degree of bowel manipulation of the duration of surgery (46–50).

Bowel motility results from coordinated contractile activity of the smooth muscle lining the gastrointestinal tract. This activity is regulated by local factors modulating smooth muscle function, by reflexes that modulate their activity through autonomic neural pathways, and by hormones and the central nervous system, which also serve to regulate bowel function. Each of these systems play a possible, independent pathogenetic role in the development of ileus and are therefore treated separately in the discussion of pathophysiology. The migrating motor complex plays a special role in postoperative ileus. The return of bowel activity marking the termination of ileus is really the resumption of the migrating motor complex activity and, thus, this phenomenon is treated independently.

Central and Systemic Factors. Regions within the brain are known to affect motility, but the contribution of brain activity to ileus remains unstudied.

Because of the association of surgery with stress, the adrenal gland was thought to mediate postoperative ileus. Indeed, plasma catecholamines are elevated following surgery (51) and high serum levels of catecholamines are associated with inhibited motility (52). Beta-adrenergic blockade improves bowel motility in experimental postoperative ileus (53). Adrenalectomy will eliminate the rise in serum catecholamines following surgery without improving postoperative ileus (19). Postoperative ileus is partially reversed by splanchnicectomy but not by adrenalectomy (54), demonstrating the importance of the sympathetic nervous system independent of adrenal activity in mediating postoperative ileus.

With stress or surgery a variety of hormones are released into the circulation. Except for the adrenal hormones, few of these have been studied directly in the context of postoperative ileus. Opiates used for analgesia cause the release of vasopressin (55). Serum levels of vasopressin are increased 14-fold following laparotomy (56). Small doses of intravenously administered vasopressin cause marked inhibition of small bowel contractility and transit in the dog (57). The mechanism of vasopressin-mediated inhibition of motility remains unclear. Vasopressin does decrease mesenteric blood flow and diminished blood flow may subsequently depress motility. Abdominal cramps frequently occur with intravenous administration of vasopressin, suggesting that peristalsis increases. The disparity between the clinical observations and experimental evidence is unexplained.

Reflex Systems. Contractility of the gut is regulated at several levels. Locally, oscillations of smooth muscle membrane potential cycle independently. Action potentials (and resulting contractions) are generated only after a threshold voltage is achieved. Exogenous influences mediate the ability of smooth muscle cells to cross the threshold and therefore regulate contractility. Release of acetylcholine by intrinsic nerves, the myenteric and mesenteric plexuses, increase motility by this mechanism. Outside of the bowel, motility is further modulated by extrinsic nerves and hormones. Parasympathetic innervation of the proximal bowel is provided by the vagus and the pelvic nerves supply the distal colon. Postganglionic sympathetic fibers follow the course of arteries into the gut and synapse with neurons in the myenteric plexus. These nerves, along with various hormones, tend only to modulate gut contractions but have no primary control. Indeed, most segments of the gut contract normally in the complete absence of extrinsic innervation. Undoubtedly extrinsic pathways play an important role in postoperative ileus, as evidenced by the inhibition of bowel function following surgery not involving the peritoneum (58). An example is hip surgery, which frequently is associated with severe ileus. Experimental evidence suggests the ileus can be duplicated by somatic nerve stimulation (59).

Parasympathetic fiber stimulation increases motility, and stimulation of sympathetic fibers inhibits it. Vagal nerve section in animals does not alter small intestinal motility, whereas splanchnic nerve division increases contractility (60). Thus, sympathetic, tonic inhibitory control predominates. Sympathetic activation occurs with stress, and surgery and is thought to significantly alter bowel motility during the postoperative period. There are high and low threshold components to the inhibitory reflex. The low-threshold system is a spinal reflex that is abolished by division of the splanchnic nerves, sectioning of the dorsal root fibers, and by anesthesia or crushing of the spinal cord. The high-threshold system requires a greater stimulus for activation, is ganglionic, and abolished by excision of the prevertebral ganglia but not affected by those manipulations that abolish the low-threshold reflex (61–66).

Experiments directed at pharmacologic deactivation of the inhibitory sympathetic neurons have supported the hypothesis that they mediate postoperative ileus. Following surgery, intestinal catecholamine stores are depleted more rapidly than in the absence of laparotomy (67). Delayed gastric emptying and small intestinal postoperative ileus following laparotomy in rats (68) are completely reversed by chemical sympathectomy with 6-hydroxydopamine (6-OHDA) (69). Similarly, inhibition of norepinephrine release by sympathetic nerve endings with bretylium has no effect on basal gastric emptying but prevents surgically induced gastric postoperative ileus in the dog (70). In dogs, Smith et al. (51) demonstrated elevated levels of plasma catecholamines after celiotomy associated with motor abnormalities (see below) and delayed gastric emptying of 7-mm undigestible spheres. The sympathetic neurons inhibit motility via α- and β-adrenergic receptors and participate in a reflex mediated by peptidergic afferents. Elimination of

peptidergic afferent fibers with capsaicin improves transit in peritonitis or postoperative ileus but does not completely abolish it (71).

Anatomic evidence for these reflex pathways exists. Sympathetic fibers provide the major inhibitory input to the bowel and provide the efferent arm of several reflex pathways. One of these pathways, a low-threshold intestinointestinal reflex, has visceral afferent fibers originating in the bowel wall with cell bodies in the dorsal root ganglia. Their axonal projections terminate on lamina I and V of the spinal dorsal horn. When activated, these fibers activate inhibitory efferent sympathetic fibers (72). Sympathetic fibers inhibit contractility by inhibiting the release of acetylcholine from excitatory fibers within the myenteric plexus. Additionally, the sympathetic efferents inhibit the neuronal release of other peptidergic transmitters within the myenteric plexus. The presence of catecholamines in the interstitial space can inhibit smooth muscle cells directly via α- and β-receptors present on their surface. Anatomic and neurophysiologic evidence exists for several potential afferent pathways. One is the same visceral fiber involved in the spinal pathway. This fiber has its substance P-containing cell body in the dorsal root ganglia and projects to the dorsal horn. However, this fiber passes through the prevertebral ganglia where axonal varicosities are present. These are thought to provide inhibitory axoaxonal or axosomatic pathways. Additionally, other afferent fibers originating within the myenteric plexus project to the prevertebral ganglia and synapse on the sympathetic ganglia.

With uncomplicated postoperative ileus, colonic motility is affected the most. Like other segments of the gut, motility is regulated by a balance between excitatory and inhibitory influences. In the proximal colon, inhibitory adrenergic fibers originating in the spinal cord and prevertebral ganglia innervate the myenteric neurons. Intramural tonic inhibitory fibers exist that are nonadrenergic and noncholinergic and whose activity is mediated by extrinsic nerves (73). Tonic inhibition prevails under most circumstances and is abolished by the α_2-adrenergic blocker phentolamine (74). Presumably α_2-receptor activation on cholinergic neurons inhibits the release of acetylcholine with consequent inhibition of smooth muscle activation and colonic motility (74). Persistent activation of this receptor system by adrenergic fibers following surgery might contribute to postoperative ileus. Some clinical evidence for this hypothesis exists. Patients with postoperative ileus treated with α-blockade combined with cholinergic stimulation achieve restoration of colonic function earlier than nontreated patients (3).

Local Factors. When the electrical activity of the stomach and small bowel is recorded, a characteristic pattern is observed. Oscillations with a fixed frequency are initiated at pacemaker centers proximally and proceed distally in an orderly manner. Occasionally, spike-wave potentials are superimposed on the oscillation plateau and are associated with contractions. Distal progress of the oscillations result from interaction of smooth muscle cells at gap junctions. Current from one cell passes to the next by ion exchange through the junction. Thus, large sheets of interconnected cells act as a syncytium so that recordings demonstrate regular oscillations of uniform amplitude. As will be discussed later, in the absence of interconnections, extracellular recordings lack periodicity and have irregular amplitude. Modulation of spike-wave activity occurs by adjusting the amplitude of oscillations: hyperpolarization inhibits, whereas decreasing resting membrane potential augments, spike-wave activity. With ileus, the lack of motility results from absence of spike waves and presumably from membrane hyperpolarization.

Anesthetic agents by themselves inhibit motility (75–80). Most anesthetic agents stabilize neural membranes and therefore have their greatest effect on portions of the bowel most dependent on neural integration. Unlike in the stomach and small intestine, smooth muscle cells in the colon lack intercellular gap junctions. Propagation of contraction is entirely dependent on neuronal systems and, therefore, is more susceptible to the inhibitory effects of anesthetic agents.

Release of endogenous opiates has been proposed as a cause of postoperative ileus. In animal studies infusion of enkephalin, a potent opiate receptor agonist, inhibits gastric contractility while increasing pyloric tone (81, 82). Small bowel myoelectric activity and propulsion are dose-dependently inhibited by morphine (83). However, treatment with the morphine-receptor antagonist naloxone does not improve postoperative bowel function. Thus, endogenous opiates do not seem important in pathogenesis of postoperative ileus (84).

While the functioning of the intrinsic nervous system of the bowel is altered, the smooth muscle itself remains viable during the period of postoperative ileus. Studies examining the contractility of

smooth muscle alone have demonstrated normal contractility during postoperative ileus in response to cholinergic agonists (21, 23, 85, 86).

Migrating Motor Complex and Integrated Electrical Activity. Transit of foodstuffs within the bowel is a process dependent upon the orderly contraction of the gut tube. This process, peristalsis, occurs by a ringlike contraction of bowel smooth muscle that progresses distally pushing the luminal contents forward. Peristaltic contractions occur in waves, sweeping the luminal contents distally. Two distinct contractile patterns exist: fed and fasting. During feeding, a variety of neural and humoral systems are activated, producing regular high-frequency powerful contractions. During feeding, this activity persist and last for several hours after the termination of the meal. Between feedings the bowel remains active but with a very different pattern of activity known as the interdigestive complex or migrating motor complex (MMC). First described by Szurszewski (87), and recently reviewed in detail by Sarna (88), this activity serves as the housekeeper of the bowel (89), periodically sweeping luminal contents distally between feedings. Unlike fed activity, these contractions occur in a periodic complex that occurs approximately once every hour or two in dogs and humans, whereas the periodicity is 10 min in rats. Initially the bowel is quiescent with smooth muscle membrane potentials oscillating as always but without associated contractions (phase I). Eventually, intermittent contractions are present, gradually increasing in power and frequency (phase II). The waves and contractions become more frequent until, for a short time, contractions occur with every membrane electrical oscillation (phase III). During this phase the luminal contents can be seen to be swept rapidly distally. The burst of activity terminates rapidly (phase IV), leading into a quiescent phase starting the cycle again (88). Interdigestive activity is of importance in postoperative ileus because patients are not fed after surgery. It is, therefore, the only impetus to bowel contraction. Clinically, duration of ileus is judged by the presence of flatus. Swallowed air is passed distally by the contracting bowel, and this occurs only when the interdigestive activity returns.

MMC activity can be temporarily abolished by some anesthetic agents in the absence of surgical manipulation (90). As demonstrated by Wright et al. (76) individual anesthetic agents differ in their effect on gut myoelectric activity. Ether totally disrupts MMC, replacing it with persistent high-amplitude contractile activity that remains for a prolonged interval following withdrawal of the drug (90). Ether also has been reported to delay (67, 78) or not effect (79) intestinal transit. Halothane also abolishes MMC activity but, unlike with ether, the bowel remains quiescent and recovers slowly after the anesthetic agent is removed. Halothane has been reported to inhibit (80) or have no effect on gastrointestinal motility (51). Enflurane increases the frequency of MMC activity with early restoration of normal activity following the termination of anesthesia. Pentobarbital increases irregularly occurring spike waves and transiently inhibit MMC activity. With pentobarbital, the MMC activity returns before the animal recovers from the anesthesia (90). Thiopental increases the velocity of propagation of electrical waves along the jejunum, but the MMC pattern is not disrupted (90). Inhalation of ethylene, cyclopropane, and halothane display only transient inhibition of small bowel transit (91), whereas intraperitoneal administration of chloral hydrate may cause profound ileus (75).

The effect of laparotomy on MMC activity is dependent upon the extent of surgery. Skin incision has no effect on MMC activity, whereas division of abdominal muscle layers causes a transient inhibition of the MMC. MMC activity is completely abolished by opening of the peritoneum, and the duration of this inhibition is prolonged if the bowel itself is manipulated. The inhibitory effects of surgery are partially blocked by spinal demedullation and completely by splanchnicectomy. No effect is seen with spinal cord transection or vagotomy (40, 90, 92). Dorsal root blockade by spinal anesthesia has been reported to improve bowel motility following laparotomy (93). Activation of the adrenergic nervous system is a well-known inhibitor of bowel motility, but in the presence of sympathectomy MMCs are still inhibited by surgery, although for a shorter period of time (92).

Studying the dog, Smith et al. (51) observed loss of the motor component of the interdigestive complex in the stomach and small bowel for 24 hr following laparotomy. This activity returned sporadically along the small bowel on the first postoperative day and in the stomach during the second. The regular activity of the complex did not return to normal for three to seven days after surgery. Return of transit, as evidenced by the movement of intraluminal spheres, occurred after resumption of phase III activity. Transit and MMC inhibition paralleled

sustained increases in plasma norepinephrine levels. Some studies have reported disordered basic electrical rhythm (76) in postoperative ileus. Immediately following surgery there is a brief period of augmented, disordered contractile activity (94) that is followed by a period of quiescence. Gradually the basic electrical rhythm returns, with normal periodicity first in the small bowel then in the colon. Initially, small bowel transit is delayed (95); then at 24 hr, the normal pattern of contractile activity returns. Colon motor activity returns in 72 hr, coinciding with the appearance of flatus (96). Gastric electrical activity remains normal during operation, but after closing the skin highly disordered activity is present. Gastric arrhythmias resolve after a short time and normal activity returns (97). Gastric electrical activity following surgery does not explain delayed gastric emptying during postoperative ileus. Possibly, pyloric tone is augmented inhibiting normal emptying (98).

The colon differs in structure and function from the rest of the bowel. Digestion and nutrient absorption that occurs in the proximal bowel does not occur; rather, the colon serves to absorb water and store feces. Proximal colon motility is antiperistaltic, serving a mixing function while water is removed from the feces. The luminal contents gradually pass distally by infrequent tonic contractions of the distal colon. Electrical activity measured at the colon surface differs from that measured in the proximal bowel. Oscillations are irregular, with quiet and noisy periods of activity that tend to be polyphasic and of irregular amplitude. However, intracellular recordings from colonic smooth muscle are similar to those from the rest of the bowel (except that contractions can occur without spike-wave activity when stimulated by certain neurotransmitters such as substance P). Structurally the colonic smooth muscle lacks gap junctions and does not function as a synctium. Surface recordings therefore reflect activity of multiple independent oscillators that do not interact. This has important ramifications for postoperative ileus. In the colon, contraction and motility is dependent upon the integration of smooth muscle activity by neural mechanisms. Normal transit cannot occur until this complex extrinsic regulatory activity recovers.

A patient's ability to tolerate feeding is predicted by the presence of flatus, an indicator of restored colonic function (99). Detailed studies of colonic motility in postoperative ileus have been made by Sarna, Condon, and coworkers in monkeys and man (48, 100, 101). Electrical activity of the colon was measured and, because of its complex nature, was analyzed by Fourier transformation (a process that breaks a signal down into its component frequencies). In the normal colon three activities were noted: electrical control activity (ECA), discrete electrical response activity (DERA), and continuous electrical response activity (CERA). The ECA occurs at discrete frequencies and represents oscillations of smooth muscle membrane potentials. The DERA are spike-wave potentials superimposed on the oscillations and are associated with contractions. CERA are sustained spike bursts of electrical activity, having no relationship with oscillations and are associated with sustained contractions that move the luminal content distally. After surgery in both monkey and man, DERA and CERA initially are absent and the ECA shifts to a lower frequency. Over the first 48 hr following surgery the ECA frequency returns to normal and DERA gradually returns, progressively increasing in duration. Approximately 72 hr after surgery, the CERA returns and is associated with the return of flatus, marking the termination of postoperative ileus.

Because of the dependence on external neural integration, the colon should be very sensitive to the effects of anesthetic agents. However, anesthesia maintained with nitrous oxide fails to inhibit colonic myoelectric activity. Enflurane and halothane diminish colonic contractile activity during the period of anesthesia, with prompt recovery following withdrawal of these agents (91). Therefore, these commonly used anesthetic agents contribute little to routine postoperative ileus resulting from the slow return of colonic motility.

TREATMENT

Symptomatic Relief. Treatment for ileus has changed little in the past 100 years. Nasogastric suction for the relief of bowel obstruction was introduced in 1884 (102) and remains the major form of therapy. Enterostomy had been utilized to relieve bowel obstruction but carried with it a 40% mortality. Wangensteen demonstrated that insertion of a nasogastric tube effectively reduced accumulation of gas and secretions, with dramatic reduction of morbidity compared to enterostomy (1). Nasogastric intubation had tremendous impact on surgical management and rapidly became the standard after abdominal procedures where ileus is a problem. It was and remains so common that,

despite subsequent studies (103, 104) failing to demonstrate the need for routine intubation, nasoenteric intubation still is routinely employed as prophylaxis.

For clinically evident ileus, nasointestinal intubation remains the only proven effective therapy. Couple with intravenous hydration or total parenteral nutrition, patients are maintained until ileus resolves spontaneously. None of the therapies listed below have been proven to be of benefit in the treatment of this disorder.

Electrical Stimulation. Like many other biologic systems, the bowel has its own intrinsic electrical rhythm. Cardiac pacing has been highly successful and, because of the similarity between cardiac and gut smooth muscle oscillations, similar techniques have been attempted in the gut. Application of electrical stimulation directly to the bowel wall with subsequent pacing has been achieved in dogs but not in the human controls (105). Electrical stimulation of the bowel was reported initially to be successful for the treatment of postoperative ileus (106) but, when compared with control patients, was proven ineffective (107, 108). Similarly, attempts to stimulate motility in the postoperative phase by the application of external magnetic energy have failed (109). Smooth muscle membrane hyperpolarization inhibits the development of spike-wave potentials during postoperative ileus. Because membrane hyperpolarization is mediated by ion channel activity, application of external electric current is not likely to overcome the hyperpolarization.

Pharmacologic Agents. Inhibition of bowel activity occurs by stimulation of the adrenergic system as well as activation of high-threshold noncholinergic fibers within the vagus. Two sympathetic inhibitory reflexes are present: one is a low-threshold spinal reflex and the second is a high-threshold peripheral reflex with synapses in the prevertebral ganglia (61). The afferent limb is incompletely understood, but some substance P-containing fibers have been implicated. The efferent is mediated by sympathetic fibers (3). Surgical stress is well known to elevate catecholamine levels, leading to inhibited bowel function after surgery. One plausible explanation for greater inhibition following surgery is that even higher catecholamine levels are found after operation than after anesthesia alone. Therefore, treatment of postoperative ileus with adrenergic inhibitors with or without cholinergic agonists has been proposed (110). Sympathetic inhibition by chemical or surgical sympathectomy partially reverses postoperative ileus in experimental animals. In dogs, Smith et al. (51) found that propranolol combined with phentolamine given in doses high enough to lower blood pressure did not improve transit following laparotomy. Even if adrenergic activation causes significant inhibition of bowel motility after surgery, utilizing conventional adrenergic blockers probably would not be effective because of their cardiovascular effects. Indeed, studies in man combining adrenergic inhibition and cholinergic activation failed to alleviate postoperative ileus (111). Alpha and beta blockade with receptor antagonists (112), guanethidine (74, 113), dihydroergotamine (114), or adrenergic depletion with reserpine may slightly improve postoperative ileus, but their use is limited by cardiovascular side effects. Bethanidine, like guanethidine, prevents the release of catecholamines and therefore mimics alpha and beta blockade. This drug had no effect on postoperative ileus when given in doses high enough to lower blood pressure 10 mm Hg (111). Alpha-adrenergic blockade with chlorpromazine or trifluperidol has been reported to be moderately successful in the treatment of postoperative ileus (61, 115). Intraperitoneal instillation of local anesthetic agents has been proposed as a means of blocking the release of inhibitory mediators. Intraperitoneal instillation of bupivacaine during laparotomy has been demonstrated to improve postoperative ileus (47).

Prostaglandins have received little attention in the treatment of postoperative ileus. There is some evidence that they inhibit the release of norepinephrine and augment the release of acetylcholine from intramural neurons (116). In the resting state, their predominant effects are direct upon smooth muscle where prostaglandins of the F and E series generally inhibit motility. However, with postoperative ileus, there is increased activity of inhibitory intramural neuron activity. Studies with PGE have demonstrated increased gastric emptying and small and large bowel transit in rats. The response varied depending upon the route of administration, intravenous being the most effective (117, 118). Intravenous infusion of $PGF_{2\alpha}$ has been reported to improve postoperative ileus (119).

Parasympathomimetic drugs will increase gut tone and contractility. Cholinergic activation improves gut transit in the rat model of postoperative ileus (120). In humans neostigmine, edrophonium, and bethanechol have been reported to improve postoperative ileus (61, 121), but the use of these

agents is limited by systemic side effects. Pantothenic acid increases acetylcholine synthesis and was proposed as a treatment for postoperative ileus (122), but controlled clinical trials failed to demonstrate improvement with this agent (123, 124).

In man, opiates given after surgery for analgesia cause no change in gastric contractility while they increase duodenal MMC activity (125). Colonic electrical response activity is increased following intramuscular administration of morphine during the postoperative period, but this activity does not propagate normally (48). Return of flatus following general anesthesia is markedly delayed by opiates (126). Opiate-receptor blocking agents have not been efficacious in the treatment of postoperative ileus (84). Avoidance of narcotics in the immediate postoperative period will lessen postoperative ileus.

Metoclopramide is a prokinetic factor that has cholinergic agonist and dopaminergic antagonist properties (12). The exact mechanism of action of unclear, but it may act by direct cholinergic activation with release of motilin. The disordered release of motilin has been implicated as a causative factor in postoperative ileus (128), although in one study intravenous infusion of motilin failed to improve postoperative ileus (129). Metoclopramide initiates phase III MMC activity by dopaminergic inhibition (130). Metoclopramide has been reported to improve (131, 132) and worsen (133) postoperative ileus.

A new prokinetic agent, cisapride, has promise for the treatment of postoperative ileus. This agent increases the force of contraction and transit in human bowel. Cisapride acts by increasing acetylcholine release in response to stimulation. Additionally, it counteracts the inhibitory effect of adrenergic nerve stimulation (134, 135). One study has demonstrated the resolution of postoperative ileus with repeated bolus injection of cisapride (136).

Cerulein is a peptide known to stimulate motility (137) by a direct action on smooth muscle. Cerulein has been reported to stimulate motility in postoperative ileus (138). Further studies with this peptide are needed.

Intraluminal irritation or exposure to hyperosmolar solutions generally increases intestinal motility. One retrospective study examined the effect of oral water-soluble contrast agents. Rapid transit of the contrast into the colon was noted with passage of stool within 6 hr of administration. Reportedly, resumption of oral alimentation was obtained within 24 hr of administration of oral contrast agents. These anecdotal results are promising, and further prospective studies need to be performed (139).

Enteral Feeding. Recently, enteral feeding, either by nasoenteric intubation or by needle jejunostomy has been promoted as a means to reduce the duration of postoperative ileus. By supplying nutrition or mechanically stimulating the small bowel, enteral feeding theoretically reduces the duration of postoperative ileus (140). Studies have reported improvement in bowel recovery with an enteral feeding regimen. However, of these, one was uncontrolled (2), and another had unusually long hospitalization times in the control group (141). One recent prospective, randomized trial of postoperative treatment with the Moss nasoenteric tube vs no specific therapy failed to reveal reduction of postoperative ileus by early postoperative feeding (142). Whether these modalities really afford an advantage in the treatment of postoperative or postoperative paralytic ileus remains to be determined. Studies evaluating the efficacy of enteral feeding regimens will need to evaluate the cost-to-benefit ratio for enteral feeding vs that of additional hospital days in the absence of such a treatment regimen.

SUMMARY

Postoperative ileus follows any operation. Although worsened if the peritoneum is entered, the length and duration of surgery does not influence the severity of postoperative ileus. Inhibitory α_2-adrenergic reflexes with peptidergic afferents contribute to postoperative ileus. Clinically, treatment of ileus centers around symptomatic relief with nasogastric suction. Trials of adrenergic blockade combined with cholinergic stimulation have met with limited success. Prokinetic drugs have not been proved effective in the treatment of this disorder. Two types of ileus exist: postoperative and paralytic. Postoperative ileus resolves spontaneously after two to three days, and probably reflects inhibition of colonic motility. Paralytic ileus is more severe, last more than three days, and seems to represent inhibition of small bowel activity. No discrete structural changes cause postoperative ileus and the role of peptidergic neuronal systems of the enteric nervous system has not been elucidated. Possible central or humoral mechanisms have not been studied extensively. The possible direct inhibition of enteric or spinal nerves by anesthetic agents not cleared from these tissues remains to be

studied. Also in need of study is the potential alteration of neurotransmitter receptor activity within the enteric nervous plexus after manipulation of the bowel.

REFERENCES

1. Wangensteen OH: The early diagnosis of acute intestinal obstruction with comments on pathology and treatment: With a report on successful decompression of three cases of mechanical small bowel obstruction by nasal catheter siphonage. West J Surg Obstet Gynecol 40:1–17, 1932
2. Moss G, Regal ME, Lichtig LK: Reducing postoperative pain, narcotics and length of hospitalization. Surgery 90:206–210, 1986
3. Neely J, Catchpole B: Ileus: The restoration of alimentary tract motility by pharmacological means. Br J Surg 58:21–28, 1971
4. Pal J: Ueber den einfluss des bauchschnittes auf die darmbewegung. Zentralbl Physiol 4:338, 1890
5. Bayliss WM, Starling EH: The movements and innervations of the small intestine. J Physiol (London) 24:99–143, 1899
6. Cannon WB, Murphy FT: The movement of the stomach and intestine in some surgical conditions. Ann Surg 43:512–536, 1906
7. Cannon WB, Murphy FT: Physiologic observations on experimentally produced ileus. JAMA 49:840–843, 1907
8. Elliot TR, Barclay-Smith E: Antiperistalsis and other muscular activities in the colon. J Physiol (London) 31:272–304, 1904
9. Olivecrona H: An experimental study of postoperative, so called paralytic ileus. Acta Chir Scand 61:485–534, 1927
10. Oshsner A, Gage IM, Cutting RA: Treatment of ileus by splanchnic anesthesia: Preliminary report of experimental study. JAMA 90:1847–1853, 1928
11. Mackay ME: The action of histamine on the motility of different parts of the intestinal tract. Am J Physiol 1030:527–536, 1930
12. McSwiney BA: Innervation of the stomach. Physiol Rev 11:478–514, 1931
13. Garry RC: The movements of the large intestine. Physiol Rev 14:103–132, 1934
14. Sealy WB, Witcher SL: Sympathetic denervation upon peristalsis of the cat small intestine in situ. Proc Soc Exp Biol Med 34:806–807, 1936
15. Ratkoczy N: Neue grundsteine zur funktionellen röntgendiagnostik des magens. Fortschr Röntgenstr 43:343–353, 1936
16. Morin G, Kofman T, Dugal PJ: Des relations du transit gastrique et de la sympathectomie abdominale totale chez le chien. CR Soc Biol 124:772–776, 1937
17. Bisgard JD, Johnson EK: The influence of certain drugs and anesthetics upon gastro-intestinal tone and motility. Ann Surg 110:802–822, 1939
18. Wakim KG, Mann FC: The effects of some intra-abdominal procedures on intestinal activity. Gastroenterology 1:513–517, 1943
19. Douglas DM, Mann FC: The effect of peritoneal irritation on the activity of the intestine. Br Med J 1:227–231, 1941
20. Wells C, Rawlinson K, Tinckler L, Jones H, Saunders J: Ileus and postoperative intestinal motility. Lancet 2:136–137, 1961
21. Arai K: Experimentelle Untersuchungen über die Meagen-Darmbewegungen bei akuter Peritonitis. Arch Exp Path Pharmakol 94:149–189, 1922
22. King CE: Studies on intestinal inhibitory reflexes. Am J Physiol 70:183–193, 1924
23. Hotz G: Beitrage zur Pathologie der Darmbewegunen. Mitt Grenzgeb Med Chir 20:257–318, 1909
24. Youmans WB, Waisman RC: Effect of beta-methylcholine-urethane on normal and on reflexly inhibited intestine. Proc Soc Exp Biol Med 39:135–140, 1938
25. Youmans WB: Neural regulation of gastric and intestinal motility. Am J Med 13:209–226, 1952
26. Wagner GA: Zur Behandlung des Ileus mit lumbal Anästhesie. Arch Gynaekol 117:336, 1922
27. Markowitz J, Campbell WR: The relief of experimental ileus with spinal anesthesia. Am J Physiol 81:101–106, 1927
28. Garry RC: The nervous control of the caudal region of the large bowel in the cat. J Physiol (London) 77:422–431, 1933
29. Burstein CL: Effect of spinal anesthesia on intestinal activity. Proc Soc Exp Biol Med 42:291–293, 1939
30. Lapointe MA: La rachianesthésie dans l'iléus aigu. Bull Mem Soc Natl Chir 53:474–478, 1927
31. Bisgard JD, Matson GM, Hirschmann J: Adynamic ileus and thermal influences on gastric and intestinal motor activity. JAMA 118:447–451, 1942
32. Wallin G, Cassuto J, Hogstrom S, Rimback G, Faxen A: Failure of epidural anesthesia to prevent postoperative paralytic ileus: Anesthesiology 65:292–297, 1986
33. Wagner GA: Behandlung der paralytischen Ileus. Berl Klin Wochenschr 56:1221–1222, 1919
34. Ochsner A, Gage IM, Cutting RA: The value of drugs in the relief of ileus. Arch Surg Chicago 21:924–928, 1930
35. Catchpole BN: Ileus: Use of sympathetic blocking agents in its treatment. Surgery 66:811–820, 1969
36. Baker, LW, Dudley HA: Auscultation of the abdomen in surgical patients. Lancet 2:517–519, 1961
37. Farrar JJ, Ingelfinger FJ: Gastrointestinal motility as revealed by study of abdominal sounds. Gastroenterology 29:789–799, 1955
38. Dahlgren S, Selking O: Postoperative motility of the small intestine. Upsala J Med Sci 77:202, 1972
39. Tinckler LF: Surgery and intestinal motility. Br J Surg 52:140–150, 1965
40. Carmichael MJ, Weisbrodt NW, Copeland EM: Effect of abdominal surgery on myoelectric activity in the dog. Am J Surg 133:34–38, 1977
41. Sabiston DC: Textbook of Surgery: The Biological Basis of Modern Surgical Practice. Philadelphia, WB Saunders, 1986
42. McPhail JL, Hardy JD, Conn JH, Shor J, Robinson S: Studies of postoperative ileus: intestinal motility as reflected in the propulsion of radiopaque materials. Surg Forum 2:471–473, 1958
43. Rothnie NG, Harper RA, Catchpole BN: Early postoperative gastrointestinal activity. Lancet 2:64–67, 1963
44. Harrower LW: Postoperative ileus. Am J Surg 116:369–374, 1968
45. Devine JA: A concept of paralytic ileus. Br J Surg 7:159–179, 1946

46. Graber JN, Schulte WJ, Condon RE: The duration of postoperative ileus related to the extent and site of operative dissection. Surg Forum 31:141–144, 1980
47. Rimback G, Cassuto J, Faxen A, Hogstrom S, Wallin G: Effect of intra-abdominal bupivicaine instillation on postoperative colonic motility. Gut 27:170–175, 1986
48. Condon RE, Cowles VE, Schulte WJ, Frantzides CT, Mahoney JL, Sarna SK: Resolution of postoperative ileus in humans. Ann Surg 203:574–581, 1986
49. Kewenter J, Kock NG: Studies on intestinal motility the first few days after partial gastrectomy and after cholecystectomy. Acta Chir Scand 125:248–253, 1963
50. Noer T: Roentgenological transit time through the small intestine in the immediate postoperative period. Acta Chir Scand 124:557–580, 1968
51. Smith J, Kelly KA, Weinshillboum RM: Pathophysiology of postoperative ileus. Arch Surg 112:203–209, 1977
52. Bernstein A, Wright AC, Spencer D: Pheochromocytoma as a cause of gastrointestinal distension. Postgrad Med J 43:180–183, 1967
53. Landman MD, Longmire WP Jr: Neural and hormonal influences of peritonitis on paralytic ileus. Am Surg 33:756–762, 1967
54. Dubois A, Henry DP, Kopin IJ: Plasma catecholamines and postoperative gastric emptying and small bowel propulsion in the rat. Gastroenterology 68:466–469, 1975
55. Weiskopf RB, Reid IA, Fisher DM, Holmes MA, Rosen JI, Keil LC: Effects of fentanyl on vasopressin human subjects. J Pharmacol Exp Ther 242:970–973, 1987
56. Cochrane JPS, Forsling ML, Gow NM, LeQuesne LP: Arginine vasopressin release following surgical operations. Br J Surg 68:209–213, 1981
57. Mitchell A, Collin J: Vasopressin effect on the small intestine: A possible factor in paralytic ileus? Br J Surg 72:462–465, 1985
58. Sarna SK: Small and large bowel motility and postoperative disorders. *In* Surgical Care II. RE Condon, J DeCosse (eds). Philadelphia, Lea & Febiger, 1985
59. Sato, Y, Terui N: Changes in duodenal motility produced by noxious mechanical stimulation of the skin in rats. Neurosci Lett 2:189–193, 1976
60. Kewenter J: The vagal control of duodenal and ileal motility and blood flow. Acta Physiol Scand 63:1–68, 1965
61. Furness JB, Costa M: Adynamic ileus, its pathogenesis and treatment. Med Biol 52:82–89, 1974
62. Furness JB, Costa M: The adrenergic innervation of the gastrointestinal tract. Ergeb Physiol 69:1–51, 1973
63. Kuntz A, Sacomanno G: Reflex inhibition of intestinal motility through decentralized prevertebral ganglia. J Neurophysiol 7:163–170, 1944
64. Youmans WB: Nervous and Neurohumerol Regulation of Intestinal Motility. New York, Interscience Publishers, 1949
65. Youmans WB: Innervation of the gastrointestinal tract. *In* Handbook of Physiology, Vol 4. CF Code (ed). Washington, DC, American Physiology Society, 1968
66. Fasano M, Waldvogel HH, Muller CA: Prevention of paralytic ileus after colonic surgery by continuous peridural sympathetic block. Preliminary report. Hel Chirurg Acta 46:245–248, 1979
67. Dubois A, Kopin IJ, Pettigrew KD, Jacobowitz MD: Chemical and histochemical studies of postoperative sympathetic activity in the digestive tract of the rat. Gastroenterology 66:403–407, 1974
68. Nilsson F, Jung B: Gastric evacuation and small propulsion after laparotomy. Acta Chir Scand 139:724–730, 1973
69. Dubois A, Weise VK, Kopin IJ: Postoperative ileus in the rat: Physiology, etiology and treatment. Ann Surg 178:781–786, 1973
70. Dubois A, Watanabe AM, Kopin IJ: Postoperative gastric ileus. Am J Dig Dis 18:39–42, 1973
71. Holzer, P, Lippe IT, Holzer Petsche U: Inhibition of gastrointestinal transit due to surgical trauma or peritoneal irritation is reduced in capsaicin-treated rats. Gastroenterology 91:360–363, 1986
72. Glise H, Lindahl BO, Abrahamson H: Reflex adrenergic inhibition of gastric motility by nociceptive intestinal stimulation and peritoneal irritation in the cat. Scand J Gastroenterol 15:673–681, 1981
73. Maggi CA, Manzini S, Meli A: Contribution of neurogenic and myogenic factors in the response of rat proximal colon to distension. Am J Physiol 252:G447–G457, 1987
74. Gillis RA, Souza JD, Hicks KA, Mangel AW, Pagani FD, Hamilton BL, Garvey TQ, Pace DG, Browne RK, Norman WP: Inhibitory control of proximal colonic motility by the sympathetic system. Am J Physiol 253:G531–G539, 1987
75. Fleischman RW, McCracken D, Forbes W: Adynamic ileus in the rat induced by chloral hydrate. Lab Anim Sci 27:238–243, 1977
76. Wright JW, Healy TEJ, Balfour TW, Hardcastle JD: Effects of inhalational anesthetic agents on the electrical and mechanical activity of the rat duodenum. Br J Anesth 54:1223–1229, 1982
77. Emmerson GA: Intestinal motility in rats anesthetized with ether. Am J Dig Dis 4:255–256, 1937
78. Reynell PC, Spray GH: The effect of ether and pentobarbitone sodium on gastrointestinal function in the intact rat. Br J Pharmacol 12:104–106, 1957
79. Ohrn PG, Johansson H, Nilsson F: Influence of ether anesthesia and oro-gastric intubation on gastric evacuation and small bowel propulsion after laparotomy. Acta Chir Scand (Suppl) 461:5–16, 1976
80. Marshall FN, Pittinger CB, Long JP: Effects of halothane on gastrointestinal motility. Anesthesiology 22:363–366, 1961
81. Konturek SJ, Thor P, Krol R, Dembinski A, Schall: Influence of methionine-enkephalin and morphine on electrical activity of the small bowel. Am J Physiol 238:G384–G389, 1980
82. Terawaki Y, Takayanagi I, Takagi K: Effects of 5-hydroxytryptamine and morphine on the stomach motility in situ. Jpn J Pharmacol 26:7–12, 1976
83. Weisbrodt NW, Sussman SE, Stewart JJ, Burks TF: Effect of morphine sulfate on intestinal transit and myoelectric activity of the small intestine of the rat. J Pharmacol Exp Ther 214:333–338, 1980
84. Howd RA, Adamovics J, Palekar A: Naloxone and intestinal motility. Experientia 34:1310–1311, 1978
85. Frey S: Experimenteller Beitrag zur Prophylaxe und Therapie der Darmlahmung. Arch Klin Chir 142:445–457, 1926
86. Zimmerman LM, Frank R, Necheles H: Effect of acetylcholine and of physostigmine on gastrointestinal motility. Observations of normal animals and of animals with experimental peritonitis. Arch Surg 33:187–196, 1936

87. Szurszewski JH: A migrating electric complex of the canine small intestine. Am J Physiol 217:1757–1763, 1969
88. Sarna SK: Cyclic motor activity; migrating motor complex: 1985. Gastroenterology 89:894–913, 1985
89. Code CF, Schlegel J: The gastrointestinal interdigestive housekeeper: motor correlates of the interdisgestive myoelectric complex of the dog. *In* Proceedings of the Fourth International Symposium on GI Motility. EE Daniel (ed). Vancouver, Mitchell Press, 1973
90. Bueno L, Ferre JP, Ruckebusch Y: Effects of anesthesia and surgical procedures on intestinal myoelectric activity in rats. Am J Dig Dis 23:690–695, 1978
91. Condon RE, Cowles V, Ekbom GA, Schulte WJ, Hess G: Effects of halothane, enflurane and nitrous oxide on colon motility. Surgery 101:81–85, 1987
92. Bueno L, Fioramonti J, Ruckebusch Y: Postoperative intestinal motility in dogs and sheep. Am J Dig Dis 23:682–689, 1978
93. Gelman S, Feigenberg Z, Dintzman M, Levy E: Electroenterography after cholecystectomy. The role of high epidural anesthesia. Arch Surg 112:580–583, 1977
94. Baker LW, Webster DR: Postoperative intestinal motility: An experimental study on dogs. Br J Surg 55:374–378, 1968
95. Wells C, Tinckler L, Rawlinson K, Jones H, Saunders J: Post-operative gastrointestinal motility. Lancet 1:4–10, 1964
96. Dauchel J, Schang JC, Kachelhoffer J, Eloy R, Grenier JF: Gastrointestinal myoelectric activity during the postoperative period in man. Digestion 14:293–303, 1976
97. Sarna SK, Bowes KL, Daniel EE: Postoperative gastric electrical control activity (ECA) in man. *In* Proceedings of the Fourth Annual International Symposium on Gastrointestinal Motility. EE Daniel (ed). Vancouver, Mitchell Press, 1973, pp 73–83
98. McCoy EJ, Baker RD: Effect of feeding on electrical activity of dog's small intestine. Am J Physiol 214:1291–1295, 1968
99. Anonymous: Postoperative ileus. Lancet 2:1186–1187, 1978
100. Sarna SK, Bardakjian BE, Waterfall WE, Lind JF: Human electrical control activity (ECA). Gastroenterology 78:1526–1536, 1980
101. Woods JH, Erickson LW, Condon RE, Schulte WJ, Sillin LF: Postoperative ileus: A colonic problem? Surgery 84:527–533, 1978
102. Kussmaul CA: Heilung von ileus durch Magenaüsspulung. Berl Klin Wochenschr 21:669–685, 1884
103. Eade GG, Metheny D, Lundmark VO: An evaluation of the practice of routine postoperative nasogastric suction. Surg Gynecol Obstet 101:275–279, 1955
104. Colvin DB, Lee W, Eisenstat TE, Rubin RJ, Salvati EP: The role of nasointestinal intubation in elective colonic surgery. Dis Colon Rectum 29:295–299, 1986
105. Richter HM, Kelly KA: Effect of transection and pacing on human jejunal pacesetter potentials. Gastroenterology 91:1380–1385, 1986
106. Bilgutay AM, Wingrove R, Griffen WO, Bannabeau RC, Lillehei CW: Gastrointestinal pacing. A new concept in the treatment of ileus. Ann Surg 58:338–348, 1963
107. Berger T, Kewenter J, Kock NG: Response to gastrointestinal pacing: Antral, duodenal and jejunal motility in control and postoperative patients. Ann Surg 164:139–144, 1966
108. Quast DC, Beall AC, De Bakey ME: Clinical evaluation of the gastrointestinal pacer. Surg Gynecol Obstet 120:35–37, 1965
109. Barker P, Allcutt D, McCollum CN: Pulsed electromagnetic energy fails to prevent postoperative ileus. J R Coll Surg Edinburgh 29:147–150, 1984
110. Smith MK, Jepson RP, Catchpole BN: Ileus: an experimental study. Br J Surg 52:381–386, 1965
111. Heimbach DM, Crout JR: Treatment of paralytic ileus with adrenergic neuronal blocking drugs. Surgery 69:582–587, 1971
112. Rada O, Stoicu G, Russo I: Influence of alpha and beta blocking agents on recovery of intestinal transit and postoperative complications in aged patients. Rev Chir 27:71–77, 1979
113. Catchpole BN: Treatment of ileus. Surgery 71:313–314, 1972
114. Thorup J, Wille Jorgensen P, Jorgensen T, Kjaergaard J: Dyhydroergotamine in postoperative ileus. Clin Pharm Ther 34:54–55, 1983
115. Petri G, Szenohradszky J, Porszasz-Gibiszer K: Sympatholytic treatment of paralytic ileus. Surgery 70:359–367, 1971
116. Ruwart MJ, Klepper MS, Rush BD: Mechanism of stimulation of gastrointestinal propulsion in postoperative ileus rats of 16, 16-dimethyl PGE_2. Adv Prostaglandin Thromboxane Res 8:1609–1610, 1980
117. Ruwart MJ, Klepper MS, Rush BD: Prostaglandin stimulation of gastrointestinal transit in post-operative ileus rats. Prostaglandins 19:415–426, 1980
118. Gromljez PF, Kaminski DL, Willman VL: The effects of prostaglandins on experimental paralytic ileus. Surg Forum 26:400, 1977
119. Fiedler L: $PGF_{2\alpha}$—a new therapy for paralytic ileus? Adv Prostaglandin Thromboxane Res 8:1609–1610, 1980
120. Ruwart MJ, Klepper MS, Rush BD: Carbachol stimulation of gastrointestinal transit in the postoperative ileus rat. J Surg Res 26:18–26, 1979
121. Kleinfeld D: Edrophonium used for vagotonic action. JAMA 223:922–923, 1973
122. Polacek MA, Close AS, Ellison EH: Double blind study of the effect of pantothenyl alcohol on experimental postoperative ileus. Surg Forum 11:325–327, 1960
123. Garvey RF, Wilson BJ: Clinical appraisal of D-pantothenyl alcohol in postoperative ileus: A double-blind study. Arch Surg 83:916–920, 1961
124. Wayne AL, Mendoza C, Rosen R, Nadler S, Case R: The role of dexanthenol in postoperative ileus. JAMA 181:827–830, 1962
125. Ingram DM, Catchpole BN: Effect of opiates on gastroduodenal motility following surgical operation. Dig Dis Sci 26:989–992, 1981
126. Yukioka H, Bogod DG, Rosen M: Recovery of bowel motility after surgery. Detection of time of first flatus from carbon dioxide concentration and patient estimate after nalbuphine and placebo. Br J Anesth 59:581–584, 1987
127. Albibi R, McCallum RW: Metoclopramide: Pharmacology and clinical application. Ann Intern Med 98:86–95, 1983
128. Rennie JA, Christofides ND, Mitchenere P, Fletcher D, Stockley-Leathard HL, Bloom SR, Johnson AG, Harding-Rains AJ: Neural and humerol factors in postoperative ileus. Br J Surg 67:694–698, 1980

129. Ruppin H, Kirndorfer D, Domschke S, Schwemmle K, Wunsch E, Demling L: Effect of 13-Nle-motilin in postoperative ileus patients: A double blind trial. Scand J Gastroenterol 39:89–92, 1976
130. Achem Karem SR, Funakoshi A, Vinik AI, Owyang C: Plasma motilin concentration and interdigestive migrating motor complex in diabetic gastroparesis: Effect of metoclopramide. Gastroenterology 88:492–499, 1985
131. Brevick H, Lind B: Anti-emetic and propulsive peristaltic properties of metoclopramide. Br J Anesth 43:400–402, 1971
132. Davidson ED, Hersh T, Brinner RA, Barnett SM, Boyle LP: The effects of metoclopramide on postoperative ileus. A randomized double-blind study. Ann Surg 190:27–30, 1979
133. Jepsen S, Klaerke A, Nielson PH, Simonsen O: Negative effect of Metoclopramide in postoperative adynamic ileus. A prospective randomized, double blind study. Br J Surg 73:290–291, 1986
134. Smout AJPM, Bogaard JW, Grade AC, Ten Thije OJ, Akkermans LMA, Wittebol P: Effects of cisapride, a new gastrointestinal prokinetic substance, on interdigestive and postprandial motor activity of the distal oesopahagus in man. Gut 26:246–251, 1985
135. Stacher G, Steinringer H, Schneider C, Winklehner S, Mittelbach G, Gaupmann G: Effects of Cisapride on jejunal motor activity in fasting healthy humans. Gastroenterology 90:1210–1226, 1986
136. Verlinden M, Michiels G, Boghaert A, de Coster M, Dehertog P: Treatment of postoperative gastrointestinal atony. Br J Surg 74:614–617, 1987
137. Bertaccini G, Agosti A: Action of Caerulein on intestinal motility in man. Gastroenterology 60:55–63, 1971
138. Agosti A, Bertaccini G, Paulucci R, et al: Caerulein treatment for paralytic ileus. Lancet 1:395, 1971
139. Watkins DT, Robertson CL: Water-soluble radiocontrast material in the treatment of postoperative ileus. Am J Obstet Gynecol 152:450–455, 1985
140. Moss G: Discharge within twenty-four hours of elective cholecystectomy. Arch Surg 121:1159–1161, 1986
141. Moss G: Postoperative ileus is an avoidable complication. Surg Gynecol Obstet 148:81–82, 1979
142. Frankel AM, Horowitz GD: Nasoduodenal tubes in short-stay cholecystectomy. Surg Gynecol Obstet 168:433–436, 1989