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Colonic Physiology

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The human colon is a dynamic organ, involved in a vast array of functions, including the absorption of water and electrolytes, the salvage of unabsorbed nutrients, and the transport of luminal contents as feces. While not an organ essential for life, the colon still plays a major role in maintaining the overall health of the human body. Understanding these physiologic principles is integral to the successful treatment – both medical and surgical – of colonic disease.

Embryology

The embryology of the colon informs its anatomy. In the third and fourth weeks of gestation, the primitive intestine arises from the cephalocaudal and lateral folding of the dorsal surface of the endoderm-lined yolk sac, forming a straight tube situated posteriorly in the embryo.1–3 Although the mucosa originates from the endoderm of the yolk sac, the muscular wall, connective tissue, and serosa have a mesodermal etiology.4 By the fourth week of gestation, the gut tube develops into three distinct regions: the foregut, midgut, and hindgut.4 The midgut begins immediately distal to the confluence of the common bile duct and the duodenum, extending to include the proximal two-thirds of the transverse colon. At the midgut, the primitive intestine maintains its connection to the yolk sac via the vitelline duct; failure of the vitelline duct to obliterate ultimately results in a Meckel’s diverticulum or a vitelline cyst or fistula.2,5 The hindgut reaches from the distal third of the transverse colon to the anal canal proximal to the dentate line. The midgut begins immediately distal to the confluence of the common bile duct and the duodenum, extending to include the proximal two-thirds of the transverse colon. At the midgut, the primitive intestine maintains its connection to the yolk sac via the vitelline duct; failure of the vitelline duct to obliterate ultimately results in a Meckel’s diverticulum or a vitelline cyst or fistula.2,5 The hindgut reaches from the distal third of the transverse colon to the anal canal proximal to the dentate line. The midgut begins immediately distal to the confluence of the common bile duct and the duodenum, extending to include the proximal two-thirds of the transverse colon. At the midgut, the primitive intestine maintains its connection to the yolk sac via the vitelline duct; failure of the vitelline duct to obliterate ultimately results in a Meckel’s diverticulum or a vitelline cyst or fistula.2,5

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The cecum – the last component to reenter the abdomen – initially is located in the right upper quadrant but then migrates inferiorly to the right iliac fossa as the dorsal mesentery suspending the ascending colon shortens and then recedes.4 As the cecal bud descends, the appendix appears as a narrow diverticulum.2–7 The loss of the dorsal mesentery of the ascending and descending colon produces their retroperitoneal fixation, absent in the cecum, transverse colon, and sigmoid colon.2

Innervation

Colonic innervation emanates from two sources: the extrinsic and the intrinsic nerves. Extrinsic innervation involves the sympathetic and parasympathetic nerves of the autonomic nervous system, which are responsible for colonic motility and sensation. Intrinsic innervation arises from the poorly understood enteric nervous system. The parasympathetic nerves primarily exert an excitatory affect upon colonic motility. The main parasympathetic neurotransmitters include acetylcholine and tachykinins such as substance P. The parasympathetic supply to the proximal colon originates from the posterior division of the vagus nerve – the tenth cranial nerve.8,9 These parasympathetic fibers reach the colon by following the branches of the superior mesenteric artery, as viewed from the front. Although the cranial limb of the herniated primary intestinal loop – the future small intestine – continues to elongate and organize into loops, the caudal limb – the proximal colon – remains mainly unaltered, its only adjustment involving the development of a cecal bud, a bulge from its antimesenteric border.3 In the tenth week of gestation, the herniated intestine commences its return to the abdominal cavity, in the process completing an additional 180° counterclockwise rotation to finalize the disposition of the embryonic proximal jejunum on the left and the primitive colon on the right.2 The cecum – the last component to reenter the abdomen – initially is located in the right upper quadrant but then migrates inferiorly to the right iliac fossa as the dorsal mesentery suspending the ascending colon shortens and then recedes.4 As the cecal bud descends, the appendix appears as a narrow diverticulum.2–7 The loss of the dorsal mesentery of the ascending and descending colon produces their retroperitoneal fixation, absent in the cecum, transverse colon, and sigmoid colon.2

input from the second to fourth sacral nerves, with the third sacral nerve the most dominant. These pelvic splanchnic nerves – the nervi erigentes – emerge from the lateral horns of S2–4. After exiting the spinal column, the preganglionic parasympathetic fibers travel superiorly and laterally, deep to the peritoneum, to join the inferior hypogastric plexus, located on the anterolateral pelvic wall, adjacent to the lateral ligaments at the level of the lower third of the rectum. The parasympathetic fibers travel superiorly and laterally, deep to the peritoneum, to join the inferior hypogastric plexus, located on the anterolateral pelvic wall, adjacent to the lateral ligaments at the level of the lower third of the rectum. From the inferior hypogastric plexus, these parasympathetic fibers are distributed to the pelvic organs and to the distal colon as far proximal as the splenic flexure. The parasympathetic fibers ultimately synapse in the bowel wall at the ganglia within the myenteric plexus of Auerbach and Meissner’s plexus.

Unlike the parasympathetic nerves, the sympathetic system effects a tonic inhibition of the nonsphincteric colonic muscle and, thus, of colonic peristalsis. Additionally, sympathetic fibers prevent epithelial secretion and reduce splanchnic blood flow. However, the sympathetic supply is excitatory to sphincter muscles, particularly to the ileocecal junction and the internal anal sphincter. The primary sympathetic neurotransmitter is norepinephrine. The inhibition of colonic tone, although not fully understood, is believed to be mediated via \( \alpha_2 \) adrenergic receptors. In one study in humans, the \( \alpha_2 \) agonist clonidine was determined to decrease fasting colonic tone, while the \( \alpha_2 \) antagonist yohimbine increased it. Stimulation of the \( \alpha_2 \) adrenoreceptor also blocked the release of acetylcholine from the hyperpolarized parasympathetic neurons in the myenteric and pelvic plexi, thus arresting parasympathetic function. In contrast, the in vivo administration of the \( \alpha_1 \) agonist phenylephrine and the \( \beta_1 \) agonist ritodrine at the highest acceptable dosages had no impact upon colonic tone. Yet, in an in vitro study, agonists of the \( \beta_1 \) and \( \beta_2 \) colonic adrenergic receptors relaxed the human taenia coli; the circular muscular tone maximally diminished after treatment with the \( \beta_2 \) agonist.

The preganglionic sympathetic effector cells are derived from the intermediolateral cell column (lateral horns) of the thoracic (T1–12) and, in particular, the lumbar spine (L1–2 or 3–4). The sympathetic nerve fibers leave the spinal column via the ventral spinal nerve roots (rami). These myelinated preganglionic fibers then exit from the ventral spinal nerve root as a white ramus communicans (“communicating branches”) to merge with the paired sympathetic trunks (paravertebral ganglia), found along the entire length of the vertebral column. Once it has joined a sympathetic trunk, the preganglionic sympathetic nerve fiber either immediately synapses at that ganglion or it ascends or descends along the trunk before synapsing at another vertebral level, from the first cervical vertebra to the first coccygeal vertebra, along the sympathetic trunk. A single preganglionic fiber synapses with 30 or more postganglionic fibers. After synapsing, the unmyelinated postganglionic fibers depart the sympathetic trunk as a gray ramus communicans, reuniting with the ventral spinal ramus, after which it is distributed to the sweat glands and arrector pili muscles of the body wall and to the smooth muscle of the blood vessels throughout the body. Yet, most preganglionic fibers – those innervating the abdominopelvic viscera – pass through the sympathetic trunk without synapsing, instead proceeding to the interconnected collateral (paravertebral or prevertebral) ganglia that lie anterior to the aorta at its junction with its main vascular branches as part of a specific splanchnic (“visceral”) nerve: the greater (T5–T9 or 10), lesser (T10–T11), least (T12), or lumbar (L1–2) splanchnic nerves. While the midgut receives its sympathetic input from the lesser splanchnic nerve, the hindgut is supplied by the lumbar splanchnic nerve. Once these preganglionic fibers synapse at a collateral ganglion, the postganglionic fibers follow the vasculature to the intestine, concluding in the enteric ganglia. Some of the postganglionic fibers terminate instead on intestinal epithelial cells, whereby intestinal secretion is inhibited. The midgut derivatives are primarily innervated by postganglionic fibers from the superior mesenteric ganglion and the hindgut structures, from the inferior mesenteric ganglion, although commingling between the ganglia is common.

The intrinsic innervation of the colon – the enteric nervous system – is uniquely able to mediate reflex behavior independent of input from the brain or spinal cord. This intrinsic network regulates the majority of colonic motility. However, the activity of the enteric nervous system is impacted by the extrinsic nerves: the sympathetic, parasympathetic, and visceral afferent nerves. This “little brain” employs the same modulators and neuro transmitters present in the central nervous system, including the excitatory acetylcholine, substance P, and neurokinin A and the inhibitory nitric oxide, adenosine triphosphate (ATP), vasoactive intestinal polypeptide (VIP), and pituitary adenyl cyclase-activating peptide. The enteric nervous system acts through many different types of neurons, with their cell bodies amassed within neuronal plexi positioned either between the circular and longitudinal muscles (the myenteric plexus of Auerbach) or in the submucosal layer. The submucosal plexi are comprised of Meissner’s plexus, situated adjacent to the mucosa, and Schabadasch’s plexus, which lies near the circular muscle. Notably, the number of neurons in the enteric nervous system greatly exceeds that of the entire autonomic nervous system. The myenteric plexus directs smooth muscle function while the submucosal plexus modulates mucosal ion transport and absorptive functions. Moreover, the enteric network influences blood flow to the colon. Control of colonic motor function via the enteric nervous system remains poorly understood at this time. However, a reflex arc is initiated by a mechanical (e.g., stretch), chemical, or other noxious stimulus, which activates an enteric primary afferent neuron; the impulse is carried to an enteric motor neuron – the effector cell – via an enteric interneuron, producing an excitatory or inhibitory effect.
Colonic Function
Salvage, Metabolism, and Storage

Although digestion and absorption primarily take place in the stomach and small intestine, the colon still plays a major role in these operations. The colon processes various complex carbohydrates and, to a lesser extent, proteins that prove resistant to digestion and absorption in the more proximal intestine.23,24 Unlike the small intestine, the colon salvages nutrients from these products via fermentation. Fermentation occurs by means of the saccharolytic and proteolytic members of the over 400 species of bacteria, the majority of which are obligate anaerobes, present within the colon.25 Approximately 10% of ingested carbohydrates enter the cecum as undigested material.11 Among the diverse end products of the bacterial fermentation of complex carbohydrates – mainly the soluble plant residues (fiber) – are the short-chain fatty acids, represented principally by butyrate (15%), propionate (25%), and acetate (60%).26 Ingestion of a diet higher in complex carbohydrates, beans, resistant starches, and soluble fiber leads to a greater output of short-chain fatty acids than that of insoluble fibers. The composition of the bacterial microenvironment also influences the amount of synthesized short-chain fatty acids.11,27 The nondigestible carbohydrate inulin – an extract of chicory – has been studied as a prebiotic, a food that selectively alters the admixture of the colonic bacterial flora; although its addition to the diet increased the proportion of beneficial bifidobacteria in the feces in various studies, its impact – whether healthful or harmful – upon other bacterial species could not be well gauged.28 Bacterial fermentation of the complex carbohydrates primarily transpires in the ascending and proximal transverse colon. In contrast, the undigested dietary proteins that reach the colon, as well as proteins from mucous and sloughed epithelial cells, are fermented in the distal colon, primarily because the carbohydrates – the preferred nutrient of most bacteria – were previously exhausted in the proximal colon; the concentration of the short-chain fatty acids produced in the distal colon is 30% less than in the proximal colon.27,29,30 However, a diet that includes prebiotics such as inulin results in a greater degree of saccharolytic fermentation in the distal colon due to the greater availability of these slowly fermentable, highly polymerized carbohydrates.27 The fermented proteins are converted into short-chain fatty acids, branched chain fatty acids, and amines. In addition, the bacterial fermentation of undigested proteins generates ammonia, phenols, indoles, and sulfurs; these possibly toxic substances are considered potential etiologic agents for such diseases as colon cancer and ulcerative colitis.27 Some of these proteolytic metabolites become a nitrogen source for bacterial growth.20,31 The residual products of the bacterial fermentation of complex carbohydrates and proteins are absorbed or, like carbon dioxide, hydrogen, and methane, passed with the feces.28 The dietary fats that reach the colon likely are not recovered in the colon but are expelled with the stool.25

The short-chain fatty acids occupy an integral position in colonic health. More than 95% of the short-chain fatty acids are created in and are immediately appropriated by the colon, with very little excreted in the feces.25,27,32 An average of 400 mmol/day, with a range of 150–600 mmol/day, of short-chain fatty acids are produced in the colon.33,34 This reclamation of undigested matter in the colon as short-chain fatty acids provides 5–15% of the total caloric needs of an individual.27 These weak acids – the preeminent colonic anions – mainly remain dissociated in the colonic lumen until absorbed either in exchange for bicarbonate via a SCFA/HCO₃⁻ transport channel; by an active transport mechanism such as the sodium-coupled monocarboxylate transporter (SMCT1) or the monocarboxylate transporter isoform 1 (MCT1); or by diffusion in their lipid soluble form.27 The sodium-coupled monocarboxylate transporter facilitates the conservation of sodium, chloride, and water in the colon.27 Furthermore, the short-chain fatty acids are incorporated as the basic elements for mucin synthesis, lipogenesis, gluconeogenesis, and protein production. In particular, propionate combines with other three-carbon compounds in the liver to participate in gluconeogenesis. Acetate is used by the liver as a component to fashion longer-chain fatty acids and by the muscle as sustenance.23,24

Although the least abundant of the short-chain fatty acids, butyrate has the greatest import in colonic homeostasis. This short-chain fatty acid acts as the primary energy source for the colonicocyte, supplying 70–90% of its energy requirements; these epithelial cells receive their nourishment solely from luminal substrates, not from the bloodstream.20,23,24 Of the short-chain fatty acids, butyrate best promotes the absorption of water, sodium, and chloride from the colon, acting as an antidiarrheal agent.27 This short-chain fatty acid also advances colonic cell proliferation and differentiation, repair, and immune function.11,27,28 Butyrate has been shown to influence colon carcinogenesis: studies have revealed that fewer butyrate transporters were present in human colonic adenocarcinomas, resulting in a decrease in the utilization of the trophic butyrate in the malignant cells.27 Moreover, in vitro studies of cancer cell lines identified apoptosis, non-proliferation, and differentiation after the administration of butyrate.27 One method by which butyrate modulates gene expression and, thus, cancer growth likely arises from its ability to suppress histone deacetylase, thus encouraging the union of various transcription factors with nuclear DNA; to modify intracellular kinase signaling; and to inhibit nuclear factor-κB.27

In the colon, many metabolic processes are influenced by functional food components. These foods – the pre- and probiotics – alter the colonic microenvironment, adding to the impact of environmental factors and genetics.33 As previously discussed, prebiotics – primarily nondigestable oligosaccharides (NDOs) – are slowly fermentable foods that selectively propagate microbial proliferation and/or activity.36 These products are completely metabolized in the
colon into short-chain fatty acids, energy, and lactic acid, leaving no nondigestable oligosaccharides in the stool. In contrast, probiotics represent active bacterial cultures that benefit the host by replenishing the colonic microenvironment. Symbiotics combine the action of pre- and probiotics. Investigations of these functional foods have focused on the lactobacilli and bifidobacteria, the growth of which transforms the colonic milieu, augmenting the immune function of the gut-associated lymphoid tissue (GALT). The effect of these supplements is thought to be attributable to an increased production of butyrate, changes in mucin production, or interference in the binding of pathogenic bacteria to the colonic mucosa. Prebiotics are particularly associated with an elevation of the concentration of short-chain fatty acids. To combat the rising incidence of antibiotic-resistant bacteria in hospitals, the World Health Organization has recommended the use of microbial interference therapies – nonpathogenic bacteria that eradicate pathogens – such as probiotics. Currently, probiotics are prescribed in cases of disturbed microbial balance, such as antibiotic-associated diarrhea. In the future, pre- and probiotics may become important supplements regularly administered to patients to promote health and to prevent illness. These functional foods further present the possibility of reducing the potential of carcinogens to form cancers.

While the colon is one organ, it demonstrates regional differences. As noted, the proximal and distal colon have different embryological origins, derived from the mid- and hindgut, respectively. In appearance, the proximal colon is more saccular and the distal colon, more tubular. The short-chain fatty acids are principally synthesized in the more acidic environment of the proximal colon. The proximal colon serves as a reservoir, in contrast to the distal colon, which mainly performs as a conduit. Yet, this truism is disputed by studies in which radiopaque markers were determined to have the same dwell time of approximately 11 h in the proximal, distal, and middle colonic segments, suggesting that the proximal colon does not preferentially operate as a receptacle for stool. Also, the character of the luminal contents impacts transit times. Large volumes of liquid pass through the ascending colon but remain within the transverse colon for as long as 20–40 h; in contrast, a solid meal is retained by the cecum and ascending colon for longer periods than a liquid diet. The salvage of water and electrolytes is primarily accorded to the proximal colon, leaving 100–150 mL in the feces. The absorption of water primarily follows a paracellular pathway, although a transcellular route involves various protein channels: aquaporins 3, 4, 5, 8, and 9. The ascending colon demonstrates the greatest absorptive capability, as the chyme resides within this segment the longest, thus maximizing its contact with the mucosa. As a consequence, diarrhea more consistently ensues after a right, as opposed to a left, hemicolectomy. Fluid retention is promoted by the antidiuretic hormone. When challenged, the proximal colon, with the additional contribution of the sigmoid colon and rectosigmoid, is able to save a further 5–6 L of intestinal water daily. Yet this facility is contingent upon the composition, rate of flow (less than 1–2 mL/min), and amount of the effluent. In the case that the absorptive capacity of the colon is exceeded, diarrheal results. Fluid secretion in the colon only transpires in the presence of diverse secretagogues, such as laxatives, bacterial endotoxins, hormones (e.g., VIP), and endogenous substances (e.g., bile acids). The colon is essential to the recovery of sodium. Under normal conditions, the colon principally absorbs sodium and chloride but secretes bicarbonate and potassium. The liquid chyme delivered to the colon contains 130–140 mmol/L of sodium whereas the concentration in stool is 40 mmol/L;...
approximately 95% of the sodium transported into the colon is conserved.29,43 If required, the colon is able to increase its salvage of sodium to 800 mmol/L/day.51 The normal colon can prevent hyponatremia even despite a diet containing as little as 1 mEq of sodium daily; in contrast, the absence of a colon encourages dehydration and hyponatremia.43 The transport mechanisms for sodium absorption, located on the luminal surface of the epithelial cells, vary throughout the colon: a Na+/H+ exchange channel in the proximal colon and an electrogenic sodium-specific channel (ENaC) in the distal colon and rectum.20 The Na+/H+ exchange channels (NHE 2 and 3) are coupled to the Cl−-HCO3− exchange channels.20 The activity of the electrogenic sodium-specific channel in the distal colon and rectum is requisite for the desiccation of stool.20 These two types of transport channel allow for the passive diffusion of sodium into the colonic epithelial cells along an electrochemical gradient, consisting of a low intracellular sodium concentration (<15 mM) and a negative intracellular electrical potential difference as compared to the lumen.40 This favorable electrochemical gradient is created by the active extrusion of sodium via the Na+/K+ ATPase pump on the basolateral membrane of the epithelial cell: three sodium ions are expelled in exchange for two potassium ions.20,30 Aldosterone, a mineralocorticoid secreted by the adrenal gland in response to sodium depletion and dehydration, enhances fluid and sodium absorption in the colon.46,50 The absorption of sodium is further promoted by somatostatin, α2-adrenergic agents (e.g., clonidine), and the short-chain fatty acids.11,24

Like sodium, chloride is recovered from the colonic lumen. In the proximal colon, chloride is traded for bicarbonate via the Cl−-HCO3− exchange channel found on the luminal surface of the epithelial cells; the activity of this channel is linked to the Na+/H+ exchange protein.20,23 However, chloride also is absorbed through a Cl−-HCO3− exchange channel that is not associated with sodium.20 Chloride absorption is supported by an acidic luminal milieu; consequentially, the concomitant secretion of bicarbonate neutralizes organic acids within the colonic lumen.24,43 The transport mechanism for bicarbonate secretion is poorly understood. Yet, bicarbonate, responsible for the alkalinity of the feces, is the primary electrolyte wasted in diarrhea.20

Potassium transport is primarily a passive process, following the movement of sodium across cell membranes. However, active potassium secretion occurs in the proximal colon and active absorption in the distal colon.11,20 The H+/K+ ATPase actively conveys potassium into the epithelial cells of the distal colon and rectum.20 A potassium channel is believed to facilitate active secretion in the proximal colon.20 Potassium secretion, combined with potassium derived from bacteria and colonic mucous, may explain the relatively high concentration of this electrolyte – 50–90 mmol/L – in stool.51,52

The colon contributes to the metabolism of urea. Approximately 0.4–1 g of urea enters the colon in the small bowel effluent daily.42 The urea is converted by the colonic microorganisms into ammonia, which is then passively absorbed by the surface epithelial cells.20,43 Ammonia is also derived from dietary nitrogen, the sloughed mucosal lining, and bacterial waste. Only 1–3 mmol of ammonia is excreted with the feces. The majority of the ammonia that reaches the colon is returned via the enterohepatic circulation to the liver, where it is refashioned into urea.30

### Colonic Motility

#### Methodology to Measure Colonic Transit

Although altered motility is thought to play a major role in various gastrointestinal disorders, surprisingly little is known about the subject. This lack of understanding arises in part from the inaccessibility of the colon, particularly the proximal colon, for direct study. Bowel questionnaires have been used to gain insight into colonic motility; however, interestingly, stool frequency – or the recollection of the patient of their stool frequency – and colorectal transit time, which represents 75% of total intestinal transit time, are poorly related.41,53,54 Early evaluations using barium were also unable to achieve a precise measurement of colonic motility.55 The initial techniques to determine colonic motility began with the calculation of colonic transit time.

#### Radiopaque Markers

One of the first methods to gauge colonic transit time involves radiopaque markers. This study, proposed by Hinton and colleagues in 1969 to assess severe constipation, follows the passage of the markers over sequential abdominal radiographs.11,56 Total and regional colonic transit times are reflected by the number and the location of the markers.11 For men, the average total colonic transit is 30.7 h (SD 3.0) and for women, 38.3 h (SD 2.9).55 Currently, the commercially available Sitzmarks™ (Konsyl Pharmaceuticals, Easton, MD) are composed of a gelatin capsule containing 24 radiopaque PVC O-rings. Various protocols for the examination exist, all of which require the cessation of all laxatives 48 h prior to swallowing the markers. In one approach that focuses on total colonic transit, 5 days after taking the capsule, an abdominal radiograph is obtained. A normal study demonstrates evacuation of 80% of the markers. The retention of more than 20% of the markers suggests slow transit constipation. Some physicians give a single capsule on Sunday evening and obtain abdominal X-rays on days 1, 3, and 5. The film on the first day provides evidence that gastric and small motility are grossly normal if all the markers are in the colon.

In order to localize the markers to specific segments of the colon – right, left, and pelvis – another technique requires that the patient consume one capsule, after which abdominal radiographs are performed every other day until all 24 markers have been expelled. As an alternative, patients...
ingest single capsules on three successive days, with only one abdominal radiograph done on day 4 of the study so as to minimize radiation exposure. The number of markers present equals the colonic transit time in hours. To better determine the distribution of the markers, some centers use capsules holding markers of different shape on each of the 3 days. An accumulation of the markers in the rectosigmoid indicates a dyssynergic defecation pattern. The reliability of the technique is affected by patient compliance as well as by differences in the interpretation of the results.

Scintigraphy

Some centers favor the more expensive colonic scintigraphy over the radiopaque marker method to measure colonic transit. As with the marker study, the protocols are not standardized among institutions. Although patients refrain from taking laxatives or opiates 24 h before the test, a normal diet is maintained throughout the study. The isotope is positioned in the cecum by the ingestion of a delayed release capsule or by orocecal intubation. The delayed release capsule, coated with the pH-sensitive polymer methacrylate, is comprised of activated charcoal or polystyrene pellets labeled with either $^{111}$In or $^{99m}$Tc. The coating dissolves at the pH of 7.2–7.4 found in the distal ileum, after which the radioactive material is delivered into the colon. Images are taken with a gamma camera at specified intervals, usually at 4, 24, and 48 h after consumption of the isotope, although this can be performed as frequently as twice daily. Segmental transit is usually determined for the ascending, transverse, descending, and rectosigmoid regions of the colon. The proportion of the counts is calculated in each section and then multiplied by a weighing factor: 0 for the cecum, 1 for the ascending colon, 2 for the transverse colon, 3 for the descending colon, 4 for the rectosigmoid colon, and 5 for stool. The results are expressed as the geometric center of the isotope mass at any given time point, with a low count indicating that the isotope is close to the cecum and a higher count that it has progressed more distally. For clinical use, the total percentage of retained isotope as compared to normal data appears to be the most convenient reporting system. Scintigraphy correlates well with the radiopaque technique in assessing colonic transit, with a similar sensitivity in diagnosing patients with slow transit constipation. The total exposure to radiation is also equivalent. Due to its greater costs, in most cases scintigraphy serves as a research instrument.

Wireless Motility Capsule

The wireless motility capsule has been proposed as an alternative method to determine colonic transit time. This technique, already proven for the study of gastroparesis, uses a capsule containing miniature pressure, temperature, and pH measurement devices. The capsule is ingested, after which continuous recordings are obtained in an ambulatory setting, with the data captured over 5 days via a wireless instrument. In one trial, the results from the capsule approach correlated well with those acquired from the radiopaque markers, with a similar sensitivity and specificity in detecting abnormal transit in those patients with constipation. The capsule is able to gauge phasic colonic contractions but not colonic motor patterns. This costly procedure is not widely employed but is attractive in that radiation exposure is avoided and patient compliance is facilitated.

Techniques to Record Colonic Motility

Colonic motility remains a constantly evolving field of study. The techniques by which colonic motility are gauged rely upon the monitoring of electrical activity or of intraluminal pressure, using surface electrodes or a manometry or barostat apparatus, respectively. This indirect assessment of colonic motility has been hindered by the instruments available for its measurement, the colonic anatomy, and the need for prolonged readings. Recordings are usually obtained over 6 h in the laboratory and over 24 h in an ambulatory setting due to the long colonic transit time, especially as compared to the small intestine. Also, the methods suffer from an absence of standardization. Although evaluations of colonic motility had initially focused upon the easily accessed distal colon, subsequent trials have indicated that this segment is not representative of the proximal colon. Yet, placement of the intraluminal devices is difficult, requiring either oral or nasal intubation or colonoscopy; furthermore, application of the surface electrodes demands surgery. Additionally, the necessity to purge the colon of stool may impact the results, producing an increase in the number of high amplitude propagated contractions, although these findings are conflicting. Determinations of colonic pressure are further influenced by artifact from extrinsic forces such as cough, straining, and sneezing. Thus, most of these approaches rest in the researchers’ domain and have not been assimilated into the standard clinical armamentarium. However, significant progress is being gained with these tools to understand the physiology and pathophysiology of colonic motility.

Manometry

Colonic manometry has been the more frequently employed method to measure phasic (brief) colonic contractions. However, few centers utilize this technique in regular practice. In this procedure, a flexible catheter – either a solid-state or a water-perfused catheter system – is inserted into the colon. It is argued that the water-perfused system increases the amount of fluid in the colon, thus altering the results. However, the solid-state catheters are fragile, expensive, and sensitive to corrosive damage from colonic irritants. However, this nonperfused system is more convenient and portable, allowing for long-term and ambulatory recordings. The validity of the readings depends upon the proper placement of the catheter. As noted, the introduction of the catheter occurs
via an oral or nasal route, confirmed with fluoroscopy, or by colonoscopy. With endoscopy, the catheter is either carried along with the colonoscope in a piggyback fashion, grasped by biopsy forceps, or is threaded over a guidewire, deposited via the colonoscope, under fluoroscopic guidance. The tip of the catheter is stationed as far proximal as the transverse colon; with direct colonoscopic deployment, the proximal transverse colon is reached in all subjects, with the probe remaining in position in greater than 80% of cases. To adhere to more physiologic conditions, unprepared colons are currently advocated, despite the impediment presented by the retained stool to the retrograde placement of the catheters; in some cases, enemas are instead used. Also, to prevent data artifact, minimal air is insufflated via the colonoscope and as much aspirated as possible during its withdrawal. The patients are often asked to maintain a diary to mark events such as bowel movements, flatus, and meals. Manometry is well able to detect the changes in intraluminal pressure after eating or the administration of a colonic stimulant (e.g., bisacodyl). However, these variations in pressure do not consistently correspond to contractions: in a study of colonic motility, the simultaneous use of manometry and colonoscopy indicated that a majority of pressure fluctuations perceived by the catheter reflected colonic relaxation, not contraction. Furthermore, manometry does not reliably identify all contractions, some of which are not associated with an appreciable pressure deflection. An investigation comparing the barostat with manometry suggested that the measurements obtained from manometry are also affected by the luminal diameter in which the tip of the device lies. However, unlike the barostat, manometry recognizes patterns of motor activity due to the multiple recording sites along the catheter.

### Barometry

The colonic barostat device addresses the inability of manometry to record colonic tone, i.e., sustained contractions. As with manometry, it is utilized clinically in few centers. The instrument includes a compressible polyethylene balloon, placed within the colonic lumen, that is attached via tubing to a barostat – a cylinder containing a piston. The balloon is maintained at a low constant pressure such that it is continuously in close contact with the colon wall in a single location. Contraction of the colon constricts the balloon, reducing its volume by forcing air into the barostat; in contrast, colonic relaxation produces an increase in the volume of the balloon so as to sustain a constant pressure. Changes in the volume of the balloon reflect colonic tone, although phasic contractions are also assessed. However, patterns of colonic activity cannot be distinguished as measurements are obtained in only one site. Unlike the manometry technique, the barostat system is capable of detecting contractions that do not produce a significant pressure change, even in colonic segments wider than 5.6 cm.

### Electrodes

Electrodes have also been applied for the study of colonic motility. These devices record the myoelectrical signals from the colon that result in muscular activity. The electrodes are placed on the serosal surface via surgery or on the mucosa by colonoscopy. The technique is seldom used due to ethical concerns.

### Peristalsis

Peristalsis represents the alternating waves of contraction and relaxation of the circular muscles of the colon wall. Fecal material is propelled antegrade through the colon by the contraction of the circular muscle proximal but the relaxation of the muscle distal to it, i.e., descending inhibition. During peristaltic activity, the saccula hausta – the product of circular muscle contraction – recede and then reform, first proximal to and subsequently at the level of the transferred material, again giving rise to colonic segmentation. The contribution of the longitudinal smooth muscle to colonic activity is unknown. The average rate of antegrade colonic transit is approximately 1 cm/h. The peristaltic reflex is thought to be initiated by luminal distention and, possibly, by chemical stimuli, which stimulate the enteric sensory neurons; ultimately, the enteric motor neurons – the effectors – are activated via the intermediary of the enteric interneurons. The interneurons may also directly detect changes in smooth muscle length. The primary neurotransmitters involved in the peristaltic reflex include the excitatory acetylcholine and the inhibitory nitric oxide and adenosine triphosphate (ATP). Although the enteric nervous network primarily controls peristalsis, the extrinsic nervous system modifies the reflex, with the sympathetic nerves suppressing and the parasympathetic nerves promoting motility, especially during defecation. Interestingly, the parasympathetic nerves also assist in the synchronization of descending inhibition. The antegrade movement of the fecal bolus is further dependent upon the radius of the colonic segment, the consistency of the feces, and the pressure differential between segments.

Colonic motility adheres to several patterns. Generally, contractions vary between tonic and phasic. The poorly understood tonic contractions are sustained events of slow onset, not necessarily inciting an elevation of the intraluminal pressure. Bassotti et al. further classify the briefer phasic contractile episodes as high and low amplitude propagated contractions and as segmental contractions. High amplitude propagated contractions – also known as migrating long spike bursts, large bowel peristalsis, and giant migrating contractions – function to transport large volumes of feces over long distances. These contractions are believed to be the manometric equivalent of mass movement – first identified on radiographic studies of the colon – whereby colonic contents are projected.
distally in seconds.\textsuperscript{40,67,80,81} The high amplitude propagated contractions transpire between 2 and 24 times a day, with an average of approximately five to six times a day.\textsuperscript{50,71} These contractions, with an amplitude of 100–200 mmHg (average of 100 mmHg), persist for 20–30 s.\textsuperscript{62,71} The contraction usually begins in the proximal colon and is transmitted distally for 15 cm or longer, with the velocity gradually increasing to as fast as 1 cm/s as the impulse moves caudad.\textsuperscript{11} A contraction that starts in the proximal colon is conveyed farther than that commencing in the distal colon: 50 cm from the cecum and 20 cm from the sigmoid colon.\textsuperscript{9} More than 95% of these contractions proceed antegrade; however, only one-third of these contractions result in the transit of fecal material.\textsuperscript{11,71,78} Moreover, not all instances of defecation, particularly those involving liquid stool, are incited by a high amplitude propagated contraction.\textsuperscript{78} High amplitude propagated contractions are considered the probable origin of the pressure spikes that occur upon morning waking (35%) and after meals (50%).\textsuperscript{71} The urge to defecate is likely attributable to these contractions.\textsuperscript{71} Borborigmy is thought also to arise from high amplitude propagated contractions.\textsuperscript{78} The impetus for these contractions is incompletely comprehended. These contractions are elicited by cholinergic medications (e.g., neostigmine), eating, colonic distention, short-chain fatty acids, and laxatives (e.g., bisacodyl).\textsuperscript{11} However, only in 50% of cases does colonic distention produce propagating activity.\textsuperscript{78} In patients with constipation, high amplitude propagated contractions are decreased in number, amplitude, extent, and speed.

The low amplitude propagated contractions are still less understood. These contractions (5–40 mmHg) – also referred to as long spike bursts – last for 3 s.\textsuperscript{71} As with the high amplitude propagated contractions, these contractions are strongly related to meals and the sleep-wake cycle. There may be an association with the passage of flatus and, in particular, liquid stool.\textsuperscript{82,83} Similar to the high amplitude propagated contractions, these contractions are likely provoked by colonic distention.\textsuperscript{71} The mechanisms by which these two propagated contractions are regulated remain unclear. However, propulsive activity depends upon a functional enteric nervous system.\textsuperscript{71}

Segmental contractions, presenting singly or in rhythmic or arrhythmic bursts, account for the majority of colonic activity, particularly at rest.\textsuperscript{78} These contractions appear with an amplitude of 5–50 mmHg.\textsuperscript{71} Found primarily in the ascending and transverse colon, this activity produces localized contractions of the circular and longitudinal muscles, in effect segregating the haustae.\textsuperscript{71} These segmental contractions, the correlate of myoelectrical short spike bursts, result in the slow, sequential antegrade or retrograde movement of colonic contents among the haustae, allowing for mixing of the material.\textsuperscript{15} Additionally, contact with the mucosal surface is maximized, which permits the absorption of intestinal water and electrolytes.\textsuperscript{71} Only 6% of segmental contractions are rhythmic, with a frequency of 2–8 cycles per minute; however, in the rectosigmoid region, a slower interval of 3 cycles per minute is predominant, possibly giving rise to a physiologic sphincter to aid in continence.\textsuperscript{9,70,83}

Unlike other mammals, humans possess a colon in which cyclic motility is absent.\textsuperscript{70} The human rectum, however, does display such cyclic activity, the rectal motor complex. The rectal motor complex is comprised of phasic contractions with amplitude of more than 5 mmHg. These phasic contractions appear at a cycle of 2–3 per minute, with each persisting for approximately 3 min. Yet, the interlude between these contractions ranges from 10 to 260 min. This phasic activity in the rectum and, potentially, the rectosigmoid may contribute to fecal continence, as it is correlated with an elevated anal canal pressure; this role is further suggested by the greater prominence of this activity at night.

Cellular Basis of Motility

Colonic motor activity is driven and coordinated by the interstitial cells of Cajal, the intestinal pacemaker cells.\textsuperscript{84} In the absence of these cells, the intestinal smooth muscle is inactive.\textsuperscript{85} The interstitial cells of Cajal arise from smooth muscle precursor cells; that is, the cells are of mesenchymal, not neuronal, origin.\textsuperscript{86} These cells are classified by their location as ICC$_{MY}$ – in the myenteric plexus, between the muscular layers; ICC$_{SM}$ – in the submucosal surface of the circular muscle; and ICC$_{IM}$ – within the circular and longitudinal muscles.\textsuperscript{87} The interstitial cells of Cajal are linked to the individual smooth muscle cells via intracellular gap junctions; the similarly coupled smooth muscle cells function as a single unit, a syncytium.\textsuperscript{9} The gap junctions allow for the passage of current – predominantly slow waves – from the interstitial cells of Cajal to the smooth muscle syncytium, leading to its depolarization.\textsuperscript{86} The interstitial cells of Cajal are believed to be mechanosensitive, able to transduce stretch stimulus from the distended colonic lumen into electrical activity.\textsuperscript{84} The ICC$_{SM}$ – the primary pacemaker cells – continuously generate high amplitude slow waves, at a frequency of 2–4 per minute, within the circular muscle layer.\textsuperscript{9} Unlike the other types of interstitial cells of Cajal, the ICC$_{SM}$ are present only within the colon, solely in its proximal portion.\textsuperscript{86} A slow wave of sufficient charge produces a smooth muscle action potential, allowing for an influx of calcium into the smooth muscle cells via the $L$-type calcium channels and, thus, a brief contraction.\textsuperscript{76} The amplitude of the slow waves is greatest at the submucosal surface of the circular muscle, diminishing while traveling through the muscular wall.\textsuperscript{89} Slow waves migrate antegrade and retrograde along short segments of the colon, rapidly in the circumferential and slowly in the longitudinal axis; as waves of different inception meet, their propagation ceases, giving rise to non-propulsive mixing activity.\textsuperscript{84,85} A second pacemaker site may involve the ICC$_{MY}$. In addition to the slow waves, the ICC$_{MY}$ may initiate low amplitude myenteric potential oscillations (MPOs) at a frequency of 12–20 per minute, which are
conveyed to the circular and longitudinal smooth muscle. The MPOs possibly are the source of propagating contractions. Moreover, the ICC<sub>MY</sub> synchronize the activity of the circular and longitudinal layers of the smooth muscle. As opposed to the ICC<sub>SM</sub>, the ICC<sub>MY</sub> are widespread throughout the colon. The etiology of the intrinsic electrical activity of the ICC<sub>MY</sub> and ICC<sub>SM</sub> is uncertain but may involve calcium regulated nonselective cation channels or large-conductance chloride channels; the oscillations from the interstitial cells of Cajal remain even the absence of extrinsic neural input. The ICC<sub>SM</sub> are thought to mediate such extrinsic input – from the enteric and autonomic neural networks – upon smooth muscle function; the release of acetylcholine and nitric oxide from excitatory and inhibitory neurons, respectively, results in alterations in the activity of the ICC<sub>SM</sub>. Furthermore, the ICC<sub>MY</sub> appear to augment the slow waves and MPOs from the ICC<sub>SM</sub> and ICC<sub>MY</sub>, respectively, as they are transmitted along the smooth muscle syncytium. Much still remains to be elucidated about the cellular basis of colonic motility.

**Characteristics of Colonic Motility in Health**

Manometry studies have demonstrated a noncyclical pattern of colonic activity. The variations in colonic activity are mirrored by changes in colonic tone. The human colon follows a circadian rhythm in which sleep is associated with its relaxation and, thus, with a marked diminution of its pressure activity. However, as previously noted, the rectum and rectosigmoid display continued phasic activity during the night. Immediately after morning waking, a two- to three-fold increase in colonic pressure activity – likely due to high amplitude propagated contractions – occurs, inciting an urge to defecate in some cases. A similar rise in colonic activity transpires during brief night-time arousals or during REM sleep. The mechanism by which the colon rapidly responds to these alterations in wakefulness is unknown. During the day, the transverse and descending colon reveal more pres- segmented contractions in close temporal relation to defecation.

### Defecation

The process of defecation involves the entire colon, not solely the anus and rectum. As already described, the majority of colonic activity – the segmental contractions – serve to retain fecal material so as to promote the salvage of intestinal water and electrolytes. However, periodically, colonic activity shifts in order to foster the expulsion of stool. Approximately 1 h prior to the act of defecation, an involuntary preexpulsive phase is initiated, in which the frequency and amplitude of antegrade nonpropagating and, particularly, propagating contractions steadily increase throughout the whole colon. The early component of the preexpulsive phase – the first 15–60 min – is characterized by propagating contractions that initially arise from the proximal colon but subsequently from the distal colon; this initial sequence is thought to transport stool into the distal colon, thus stimulating distal colonic afferent nerves, which in turn provoke further propagating sequences. During the late phase, consisting of the last 15 min, the point of origin of these contractions reverses from the distal to the proximal colon. Scintigraphic studies reveal that, in one bowel movement, 20% of the ascending colon can be emptied; other evaluations indicate that nearly the entire colon may be evacuated of stool in a single defecatory action. A number of investigations identified antegrade high amplitude propagated contractions in close temporal relation to defecation; in contrast, proteins inhibit motor function.
Colonic Sensation

Colonic sensation has proved a complicated, poorly understood topic. The normal physiologic processes of the healthy colon are largely unnoticed, with only fullness and an urge to defecate consciously perceptible. Afferent nerve fibers reach the central mucosa of the colon while Pacinian corpuscles are found in the mesentery. Afferent nerve fibers reach the central nervous system via parasympathetic pathways and spinal afferent nerves, both of which display mechano- and chemosensitivity. The parasympathetic fibers convey sensory information from the proximal colon via the vagus nerve to cell bodies in the nodose and jugular ganglia and, from the distal colon, by the pelvic splanchnic nerves. The precise role of the parasympathetic afferent fibers remains unknown but likely involves unconscious reflex sensation, not painful stimuli. Sensory input from the colon is chiefly detected by spinal afferent neurons, primarily by those with their cell bodies within the lumbar dorsal root ganglia. These lumbar spinal afferent nerves travel with the sympathetic fibers within the lumbar splanchnic nerves from the colon by way of the inferior mesenteric ganglia. The lumbar spinal afferent fibers conclude in sensory endings throughout the entire large intestine, whereby pain, colorectal distention, mesenteric traction, and noxious mucosal stimuli are discerned. In contrast, the sacral spinal afferents, with their cell bodies in the sacral dorsal root ganglia of S2–4, are thought to be concerned with a sensation of rectal fullness and an urge to defecate. These sacral spinal afferent fibers are borne along with the parasympathetic pelvic splanchnic nerves.

Visceral pain sensation is carried by rapidly conducting Aδ fibers or by unmyelinated C fibers. The Aδ fibers are associated with the more localized “discriminative” pain, which persists for as long as the stimulus, and the C fibers in the diffuse “affective-motivational” pain, which continues beyond the duration of the catalyst. Sensory information is transported to the brain along the spinothalamic and spinoreticular tracts as well as by the dorsal column of the spinal cord. The spinothalamic tracts specifically transmit sensation from the Aδ and C fibers to the somatosensory cortex via the lateral thalamic nuclei or to the frontal, parietal, and limbic regions by means of the medial thalamic nuclei, respectively.

The modulation of visceral sensation occurs through several methods. Enteroenteric reflexes mediated by the spinal cord produce variations in the smooth muscle tone, leading to changes in the activation of the nerve endings in the intestine or mesentery. The perception of visceral pain is influenced by descending noradrenergic and serotonergic pathways that emanate from the reticular formation, hypothalamus, and frontal cortex. These fibers project to the dorsal horn of the spinal cord, where they modify noxious input from the visceral afferent nerves. This mechanism likely explains the experience of wounded soldiers who feel no pain in the midst of battle. The intersection of visceral spinal afferent nerves with somatic afferent nerves in the dorsal horn of the spinal cord produces the phenomenon of referred pain, in which visceral sensation is consciously recognized as somatic pain, located in a dermatome of the same embryologic origin as the visceral structure: T8–T12 for the midgut and T12–L2 for the hindgut. In addition, visceral afferent nerves from the colon relay information via collaterals to the reticular formation and thalamus, which induce alterations in affect, appetite, pulse, and blood pressure through autonomic, hypothalamic, and limbic system connections.

Disturbances in Colonic Physiology

Physiology of Constipation

Constipation is a common complaint, with a prevalence of 2–28% among Western populations. This disorder refers to infrequent bowel movements (fewer than three per week); hard or lumpy stools; incomplete evacuation; a sensation to infrequent bowel movements (fewer than three per week); hard or lumpy stools; incomplete evacuation; a sensation of anorectal obstruction; the need for manual maneuvers to facilitate defecation; and/or excessive straining. Individuals with constipation are an incredibly heterogeneous group. Distinct subtypes of constipation exist, each requiring different treatment modalities; however, even within these subtypes, there may be wide variability in the clinical presentation and pathophysiologic etiology. The causes for constipation range from dietary, pharmacologic, structural, to systemic.

Many people become constipated due to dietary and lifestyle neglect. In the USA, fiber intake is overall low. Two primary roles of the colon, solidifying liquid chyme into stool and defecation, are dependent upon adequate dietary fiber: dietary fiber “normalizes” large bowel function. In particular, the bulkier stool produced by fiber supplementation stimulates propulsive activity, thus decreasing colonic transit time. The recommendation for adequate fiber intake ranges from 20 to 35 g/day for adults. For an individual on a 1,500–2,000 kcal/day diet, in order to include 15 g of fiber, 11 servings of refined grains and 5 servings of fruits and vegetables must be consumed. Fiber is classified as either soluble or insoluble, acting by differing mechanisms to...
increase stool weight. Soluble fibers such as oat bran provide rapidly fermentable material to the proximal colon, which allows for sustained bacterial growth.\textsuperscript{108} The consequent higher bacterial content of the stool results in the greater fecal mass.\textsuperscript{108} In an average bowel movement, 50% of the stool weight consists of bacteria.\textsuperscript{103} Also, soluble fibers cause a rise in the excretion of lipids and fats, further boosting stool weight.\textsuperscript{103} In contrast, poorly fermentable insoluble fibers such as wheat bran, cellulose, and lignin augment stool weight by providing more undigested plant material for evacuation.\textsuperscript{108} One gram of wheat bran generates 2.7 g of stool.\textsuperscript{103} Wheat bran also promotes fat excretion, but not to the extent of oat bran.\textsuperscript{108} The outcomes of fiber supplementation as a treatment for constipation have yielded conflicting data.

Constipation may be seen more commonly in sedentary individuals. The Nurses Health Study suggested that those women who engaged in daily strenuous activity were 44% less likely to experience constipation than those who exercised less than once a week.\textsuperscript{109} During exercise, phasic and propagating motor activity is diminished in the colon, with the effect more pronounced with more vigorous effort; however, after the physical exertion is completed, an increase in the frequency and amplitude of the propagating pressure waves is demonstrated, possibly due to the restoration of parasympathetic input.\textsuperscript{68} This postexercise pattern may precipitate the propulsion of feces.\textsuperscript{66} During or after exercise, individuals often report an urge to defecate or defecation itself.\textsuperscript{109} In fact, abdominal cramps and diarrhea are frequently related by runners.\textsuperscript{109,111} However, in a small study of the impact of regular exercise – 1 h a day, 5 days a week – upon chronic idiopathic constipation, there was no symptomatic improvement in the eight subjects after 4 weeks of increased activity.\textsuperscript{112} Moreover, a small study examining colonic transit in otherwise sedentary men after mild exercise, consisting of 1 h of walking on a treadmill for 3 days/week, showed no significant difference in the passage of radiopaque markers as compared to baseline.\textsuperscript{113}

Idiopathic slow transit constipation involves ineffectual colonic propulsion, resulting in a measurable delay in the movement of fecal material through the colon. The severity of the presentation is variable, with the most intractable cases referred to as colonic inertia. These patients with slow transit constipation, usually women, have fewer than one bowel movement per week, often in association with abdominal pain, a lack of an urge to defecate, malaise, fatigue, or bloating.\textsuperscript{103} Little benefit is gained from dietary fiber supplementation, which, conversely, may cause worsened constipation, or from laxatives.\textsuperscript{103} The symptoms often arise during puberty and steadily deteriorate over time.\textsuperscript{103} Retarded colonic transit in these individuals is either pan-colonic or segmental.\textsuperscript{66} Slow transit constipation is consistently affiliated with a blunted colonic motor response to eating (i.e., gastrocolic reflex), including both propulsive and segmental contractions.\textsuperscript{66,64,83} In contrast, in patients with colonic inertia, there is no colonic response to a meal.\textsuperscript{103} A significant decrease in the frequency as well as the amplitude of high amplitude propagated contractions is demonstrated in slow transit constipation, leading to reduced colonic propulsive activity.\textsuperscript{41,64,71,114,115} Furthermore, the preexpulsive phase of the defecatory process is depressed.\textsuperscript{103} Conflicting results have been obtained from investigations into excessive, disorganized rectosigmoid phasic activity – a “brake” to antegrade propulsion – as a factor in slow transit constipation.\textsuperscript{60,64}

Histological evaluations reveal a marked decrease in the population of myenteric plexus neurons; however, of the neurons present in the myenteric plexus, those that produce the potent inhibitory neurotransmitter nitric oxide are vastly predominant, especially as compared to controls.\textsuperscript{116} Slow transit constipation also features a significant reduction in the interstitial cells of Cajal either throughout the colon or solely in the sigmoid colon.\textsuperscript{54,117,118} Moreover, the morphology of the existing cells is seen to be strikingly abnormal, demonstrating few dendrites and an irregular surface.\textsuperscript{103} Colonic transit studies of slow transit constipation reveal retention of more than 20% of the radiopaque markers 5 days after their ingestion.\textsuperscript{103}

Obstructed Defecation

Obstructed defecation usually results from abnormalities in pelvic as opposed to colonic function. Typically, this disorder is associated with failure of the puborectalis muscle to relax during defecation, producing a functional – not a physical – obstruction.\textsuperscript{11} Anatomic abnormalities also causing obstructed defecation include rectocele, enterocele, excessive perineal descent, and rectal intussusception. These patients report inordinate straining, incomplete evacuation, painful defecation, infrequent bowel movements, and digital anal disimpaction.\textsuperscript{103} Among the diagnostic tests for obstructed defecation are anorectal manometry or electromyelography, balloon expulsion, barium defecography, and dynamic MRI. A defecogram may identify retention of 50–100% of the instilled barium in the rectum of patients with obstructive defecation.\textsuperscript{58} Colonic transit studies in these patients demonstrate collection of six or more radiopaque markers in the distal colon, indicating partial evacuation of the rectum.\textsuperscript{58,119} Two-thirds of patients with obstructive defecation may display a concurrent pattern of slow transit constipation.\textsuperscript{58}

Obstructed defecation rarely arises from a colonic source – a sigmoidocele. In this variant, a redundant sigmoid colon descends into the rectovaginal pouch (of Douglas) during defecation, impinging upon the rectum during attempted evacuation.\textsuperscript{120} In one study of 463 patients with constipation, fecal incontinence, or chronic idiopathic rectal pain, a sigmoidocele was diagnosed on defecography in 5.2%.\textsuperscript{120} Defecography is the primary method of diagnosis of a sigmoidocele. The severity of a sigmoidocele is determined by the extent of its decline into the pelvis, as compared to the pubococcygeal and ischiococcygeal lines.\textsuperscript{120}
While third degree sigmoidoceles likely benefit from a sigmoid colectomy, the significance and optimal management of first and second degree sigmoidoceles are not fully understood. The clinician should also be cognizant of concomitant pelvic floor disorders in these patients.

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a functional disorder with multiple manifestations: constipation-predominant (IBS-C), diarrhea-predominant (IBS-D), and mixed (IBS-A). Irritable bowel syndrome is characterized by altered bowel habits and chronic, recurring abdominal pain directly related to defecation, in the absence of an anatomic abnormality. Extra-colonic complaints include lower back pain, lethargy, nausea, urinary symptoms, dyspareunia, and dysmenorrhea. The etiology of irritable bowel syndrome is unclear but is believed to involve visceral hypersensitivity to intraluminal stimuli. Aberrant motility, inflammation, anomalies in extrinsic autonomic innervation, abnormal brain–gut interaction, and the role of psychosocial factors have also been extensively investigated. Hormonal factors may be involved, as symptoms are often increased perimenstrually; however, the complaints persist even in the absence of menses. The treatment of IBS is based on the nature and severity of symptoms. Education, reassurance, and the elimination of foods that incite the typical complaints are the initial interventions. In some patients, fiber supplementation exacerbates the IBS. For those who do not respond to conservative measures, medication is considered. However, the pharmacologic therapy of IBS-A has not been well studied.

In approximately one-third of patients with irritable bowel syndrome, constipation is the main feature (IBS-C). Women are primarily affected by IBS-C. The majority of these patients demonstrate normal colonic transit and motility patterns, although there is a possible overlap with slow transit constipation. Tegaserod, an agonist of the 5-HT4 receptor that is involved in the metabolism of serotonin, showed promise as a treatment of IBS-C but was withdrawn by the Food and Drug Administration in 2007 due to a high incidence of myocardial infarction, stroke, and unstable angina. In some studies, probiotics such as Lactobacillus and Bifidobacterium produce variable degrees of alleviation of IBS symptoms such as pain.

Lubiprostone (Amitiza®, Sucampo Pharmaceuticals, Inc., Bethesda, MD), a prostaglandin E1 analog, activates type 2 chloride channels on the apical membrane of colonic epithelial cells. This medication promotes intestinal fluid secretion and, indirectly, colonic motility in patients with IBS-C. Studies of lubiprostone revealed significant improvement in stool frequency and consistency, abdominal discomfort and pain, straining, and bloating. Cholecystokinin, found in elevated levels in the plasma and sigmoid colon of IBS-C patients, has been implicated in the pathogenesis of IBS: infusion of cholecystokinin induces typical symptoms of irritable bowel syndrome. However, in a randomized trial, the CCK-1 receptor antagonist dexloxiglumide led to no amelioration in IBS symptomology; moreover, overall colonic transit was unchanged, although emptying of the ascending colon was delayed. However, a pilot study of a similar CCK-1 receptor antagonist, loxiglumide, yielded some improvement in IBS symptoms. A randomized trial of neurotrophin-3, a protein growth factor integral to the development of the enteric nervous system, in constipated patients revealed more frequent spontaneous bowel movements, a more rapid colonic transit time, and a reduction in associated symptoms. Approximately one-third of subjects experienced transient injection site reactions after subcutaneous administration.

Diarrhea-predominant irritable bowel syndrome is encountered in approximately one-third of patients with IBS. The majority of men with irritable bowel syndrome experience the diarrhea-predominant type. This subtype is often affiliated with urgency and fecal incontinence. IBS-D may follow an episode of acute gastroenteritis, pelvic surgery, or emotional stress. Some patients with IBS-D display accelerated proximal colonic transit, with an increased frequency of high and low amplitude propagated contractions. Rectal hypersensitivity is also a feature in some of these patients. Antispasmodics such as hyoscine are prescribed for those with abdominal pain and bloating, especially after meals. Low-dose tricyclic antidepressants (e.g., amitriptyline) are added when the pain is more constant and even disabling; these medications function not as mood stabilizers but instead act directly on the gut and central pain processing. Loperamide is an antidiarrheal agent safe for long-term use. Diarrhea is effectively addressed by selective serotonin 5-HT4 antagonists such as Alosetron. This drug was initially FDA approved in March 2000, only to be retracted due to reports of ischemic colitis, severe constipation, and even death. In June 2002, it was adopted solely for women with chronic, severe IBS-D. However, the medication may only be supplied by physicians participating in the Prometheus Prescribing Program, after the patient signs a patient–physician agreement. Further investigation into these novel pharmaceuticals for IBS is required.

Ogilvie’s Syndrome

Ogilvie’s syndrome, initially described in 1948, is also known as acute colonic pseudo-obstruction. This disorder is characterized by an imbalance of autonomic innervation to the colon: the inhibitory sympathetic input exceeds that of the excitatory parasympathetic nerves. A massively
dilated colon – particularly the proximal colon – results from the consequent suppression of peristaltic activity.\textsuperscript{136} The specific source for the initial motor disturbance that allows for this scenario is unknown.\textsuperscript{136} One hypothesis ascribes this functional obstruction to impairment of the pelvic (parasympathetic) splanchnic nerves supplying the distal colon, giving rise to an atonic segment, lacking peristaltic function.\textsuperscript{136} Acute colonic pseudo-obstruction has been reported concurrent with infectious or inflammatory (e.g., acute pancreatitis), cardiovascular (e.g., myocardial infarction), metabolic (e.g., hypokalemia), postoperative (e.g., spinal or pelvic surgery), posttraumatic, neurologic (e.g., Alzheimer’s disease), respiratory (e.g., pneumonia), and neoplastic causes (e.g., metastatic disease); drugs (e.g., antidepressants); and old age.\textsuperscript{136} As indicated by the law of Laplace (wall stress = [(transmural pressure)×(radius)]/wall thickness), the cecum is at greatest risk of perforation in light of its thin wall and large diameter.\textsuperscript{137} Despite symptoms and signs consistent with a large bowel obstruction, no mechanical blockade is present. The management of Ogilvie’s syndrome begins with eliminating the presence of a physical obstruction with a water-soluble contrast enema. In the majority of cases, colonic dilatation responds to conservative therapy, including nasogastric decompression, correction of fluid and electrolyte abnormalities, cessation of antimotility medications such as opiates, and remedy of the underlying illness.\textsuperscript{138} In the absence of peritoneal signs or a cecal diameter greater than 12 cm on radiographic studies, conservative measures may be continued for 48–72 h. This approach is associated with a 14% mortality rate.\textsuperscript{136} The colon may also be mechanically decompressed via colonoscopy, although in one study, this difficult procedure in an unprepared colon was affiliated with a 1.7% morbidity and a 3.4% mortality rate; yet, colonoscopic decompression was successful in 79.3% of cases, albeit with a recurrence in 20% of patients.\textsuperscript{139} Pharmacologic treatment has become the mainstay of management for acute colonic pseudo-obstruction if conservative measures fail. Neostigmine (2–2.5 mg IV over 1–60 min), an acetylcholinesterase inhibitor, provides a surfeit of acetylcholine to the enteric muscles and the neuromuscular junctions, thus inducing propagating contractions, specifically high amplitude propagating contractions, and the prompt evacuation of stool.\textsuperscript{136} Administration of neostigmine may produce bradycardia, abdominal pain, vomiting, and excessive salivation.\textsuperscript{138} Alternative, less-studied pharmacologic treatments are comprised of 5-HT\textsubscript{4} receptor agonists (e.g., cisapride), motilin receptor agonists (e.g., erythromycin), muscarinic receptor agonists (e.g., bethanechol), neurotrophins (e.g., NT-3), nitric oxide synthase inhibitors (e.g., nitro-L-arginine methyl ester), and somatostatin analogs (e.g., octreotide).\textsuperscript{136} Surgical treatment – a cecostomy tube or a subtotal colectomy – is a final option if less invasive techniques are unsuccessful. Even in a nonemergent setting, surgery has a 30% mortality rate.\textsuperscript{136} However, failure to decompress the colon may yield cecal ischemia and/or perforation in 14–40% of cases; the mortality of these patients increases to 40–50%.\textsuperscript{136}

Implications of Colonic Physiology for the Surgeon

Why is an understanding of colonic physiology important for the surgeon? Knowledge of the embryologic development of the colon is essential when considering nerve preservation, vascular supply, and resection margins during colectomies. The poorly understood topic of colonic motility impacts surgeons, particularly in the phenomenon of postoperative ileus. In a murine model of postoperative ileus, a reduction in the number of interstitial cells of Cajal was evident on both sides of the colonic anastomosis within hours of the surgery; as a consequence, fewer slow waves were identified in that particular segment, possibly giving rise to postoperative ileus.\textsuperscript{88} Various disorders of colonic motility may stem from abnormalities of the interstitial cells of Cajal. These cells are significantly depleted in the colons of patients with diverticulosis and with slow transit constipation.\textsuperscript{141} As basic science research advances, the surgeon ultimately will be called upon to evaluate and apply novel pharmaceuticals to reduce the impact of postoperative ileus as well as to treat other disorders of colonic motility. Surgeons also will invariably be consulted to assess the suitability of surgical management for abnormalities of colonic motility such as colonic inertia and intractable constipation.

The resection of a portion or the entirety of the colon can have profound functional ramifications for the patient. Prior to a colectomy, the surgeon optimally should discuss these possible outcomes with the patient. Postoperatively, the physiologic consequences of a colectomy must be managed. For instance, a patient with a new ileostomy requires counseling regarding adequate fluid and salt intake to compensate for the loss of the colon. Furthermore, defecatory dysfunction – frequent bowel movements, urgency, or soiling – may occur after a low anterior resection. Subsequent to the procedure, injury of the parasympathetic pelvic splanchnic nerves due to dissection around the inferior mesenteric artery may produce a denervated colonic segment with an increased colonic transit time and a greater proportion of nonpropagating contractions.\textsuperscript{142} The neorectum demonstrates a decline in compliance postoperatively, although the maximum tolerated volume returns to normal 6 months later.\textsuperscript{143} Yet, the volume needed to elicit the recto-anal inhibitory reflex is persistently reduced even 1 year after surgery.\textsuperscript{143}
Conclusion

The colon has proven an enigmatic organ. Its major roles – the salvage of intestinal water and electrolytes, the storage of fecal material, and the production of short-chain fatty acids – seem unambiguous. However, the mechanisms underlying its physiologic and pathophysiologic processes remain difficult to define. Although not essential for life, its normal function is integral to our well-being.

References

2. Colonic Physiology


127. Zehnorn (tegaserod maleate) Information. US Food and Drug Administration; 2009.


The ASCRS Textbook of Colon and Rectal Surgery
Second Edition
Beck, D.E.; Roberts, P.L.; Saclarides, T.J.; Senagore, A.J.;
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