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ABSTRACT

This collaboration of two physiologists and a gastroenterologist provides medical and graduate students, medical and surgical residents, and subspecialty fellows a comprehensive summary of digestive system physiology and addresses the pathophysiological processes that underlie some GI diseases. The textual approach proceeds by organ instead of the traditional organization followed by other GI textbooks. This approach lets the reader track the food bolus as it courses through the GI tract, learning on the way each organ's physiologic functions as the bolus directly or indirectly contacts it. The book is divided into three parts: (1) Chapters 1–3 include coverage of basic concepts that pertain to all (or most) organs of the digestive system, salivation, chewing, swallowing, and esophageal function, (2) Chapters 4–6 are focused on the major secretory organs (stomach, pancreas, liver) that assist in the assimilation of a meal, and (3) Chapters 7 and 8 address the motor, transport, and digestive functions of the small and large intestines. Each chapter includes its own pathophysiology and clinical correlation section that underscores the importance of the organ's normal function.

KEYWORDS

gastrointestinal physiology, digestion, motility, absorption, secretion, esophagus, stomach, pancreas, liver, biliary system, intestines, colon, gastrointestinal hormones, enteric nervous system

Contents

Preface

Over 35 years ago, we (Neil Granger, James Barrowman, Peter Kvietys) undertook the task of producing a textbook of medical physiology that focused exclusively on the digestive system. The resulting monograph, entitled *Clinical Gastrointestinal Physiology*, was published in 1985 by the W. B. Saunders Company. The textbook was produced for use in physiology courses offered to medical and graduate students, and as refresher material for medical or surgical residents, subspecialty fellows, and for the faculty assigned the task of teaching gastrointestinal physiology to these trainees.

When the initial version of this textbook was produced, GI physiology was commonly taught as part of a larger, comprehensive medical physiology course that covered the function of all body systems, and it devoted relatively little attention to pathophysiology and the clinical manifestations of GI dysfunction. A recent trend in medical education has resulted in the systems-based, integrated medical curriculum, wherein there is no longer an identifiable course in physiology. Consequently GI physiology is now often taught as part of a course that integrates basic science and clinical aspects of the digestive system, with a goal of bridging the gap between theory and practice, and helping take physiology from "bench to bedside."

The science of GI physiology has expanded quite remarkably over the past 35 years. Advancements in the field of biomedicine and the development of new high resolution imaging technology have greatly improved our understanding GI physiology at the molecular, cellular, and organ levels. These advances have also led to a more rational view of the molecular basis of the different pathological processes that affect the digestive system.

With the rapid expansion of knowledge on the digestive system and the emphasis placed on integration of basic and clinical material in the new medical curriculum structure, there is a clear need for a textbook that provides comprehensive and up-to-date coverage of digestive system physiology that highlights medical relevance of the physiological principles with discussions of pathophysiology and clinical correlation. Accordingly, we have extensively revised and updated this textbook material, which was first published in 1985. The underlying concepts of physiology presented in this text will help the clinical learner to develop a broader understanding

of the digestive system to approach clinical challenges with the strength of a physiological approach to treatment.

We have retained the organizational feature of the original book that presents the physiologic concepts for the individual organs of the digestive system, rather than the more traditional organization in terms of the major GI functions, that is, motor, absorptive, and secretory functions. This approach allows the reader to follow a bolus of food down the GI tract and learn the physiologic functions that the bolus contacts, either directly or indirectly (e.g., pancreas, liver). It also serves to emphasize the sequential nature of the actions of each organ in the digestive system and places into perspective the contribution of each organ to the overall assimilation of a meal.

The textbook is divided into three parts. The first part (Chapters 1–3) includes coverage of basic concepts that pertain to all (or most) organs of the digestive system, salivation, chewing, swallowing, and esophageal function. The second part (Chapters 4–6) is focused on the major secretory organs (stomach, pancreas, liver) that assist in the assimilation of a meal, whereas the third (Chapters 7 and 8) addresses the motor, transport, and digestive functions of the small and large intestines.

The authors are very grateful to Janice Russell for her expert and timely production of the original illustrations that appear in this textbook.

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Dedication

To James A. Barrowman, MD, PhD
(1936–1991)

CHAPTER 1

Basic Concepts

INTRODUCTION

The energy required by all organisms for continued existence is derived from nutrients assimilated from the environment. Although single-celled organisms obtain these nutrients by simple processes, such as diffusion and phagocytosis, a more complex and specialized system exists for this purpose in multicellular organisms. In humans, this system takes the form of a tube, referred to as the gastrointestinal tract; the internal surface of which constitutes the largest interface between the external environment and the body's internal milieu. The gastrointestinal tract is richly supplied by blood vessels of the circulatory system, which distribute the assimilated nutrients to all tissues of the body.

The gastrointestinal tract (Figure 1-1) consists of a tube from mouth to anus (oropharynx, esophagus, stomach, and small and large intestine) and is associated with several secre-

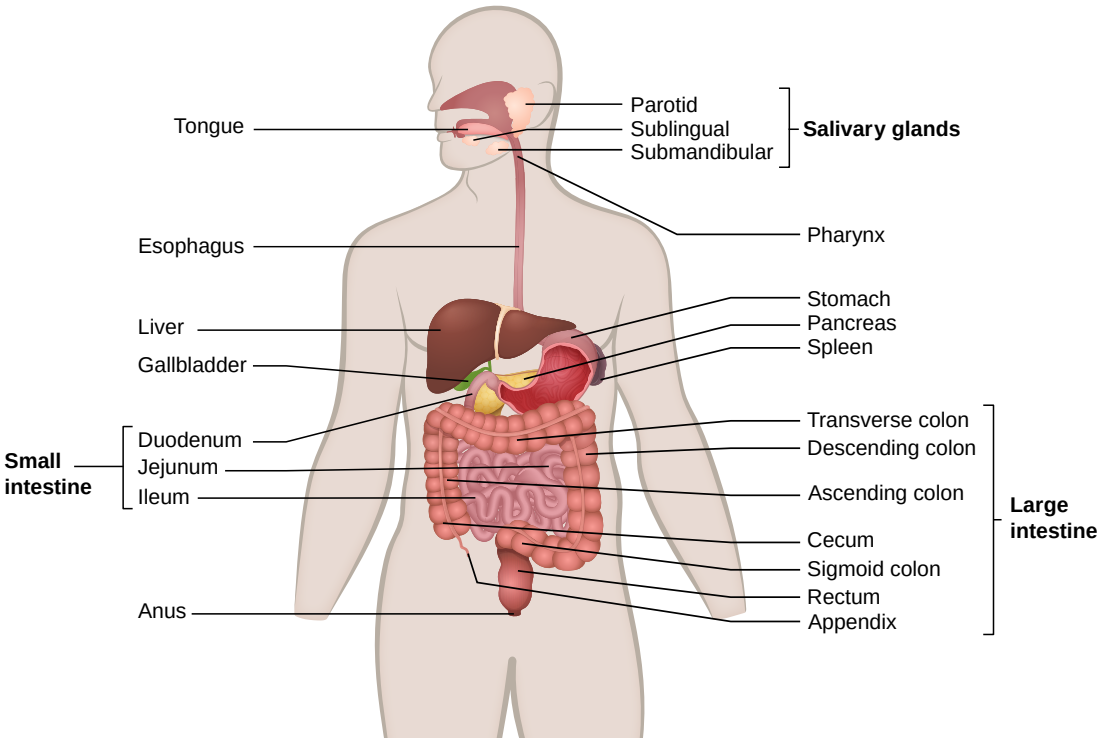

FIGURE 1-1: The digestive system includes the mouth, esophagus, gastrointestinal tract, and accessory organs, that is, the salivary glands, liver, gallbladder, the pancreas.

tory organs (salivary glands, liver, pancreas). Most of these components make a specialized contribution to the overall process of assimilation, that is, digestion and absorption, whereas other components simply store or propel food. The mouth and esophagus are primarily involved in food propulsion. The stomach and colon are mainly involved in the storage of food and food residues, respectively. The salivary glands, pancreas, and liver manufacture and deliver digestive juices, whereas the primary site of digestion and absorption of food is the small intestine.

The medical significance of the digestive system is verified by the fact that a large proportion of patients self-treat with over-the-counter products and consult their physicians concerning symptoms referable to the gastrointestinal tract. Common symptoms, such as indigestion, nausea, vomiting, heartburn, abdominal discomfort/pain, flatulence, constipation, and diarrhea, frequently reflect disorders of function. Nevertheless, a significant proportion of these symptoms may indicate underlying disease processes. Gastrointestinal disorders translate into high medical costs (direct and indirectly due to disability) and many hours of diagnostic effort on the part of the physician. It is essential that the normal functions of the digestive system be understood before the physician can effectively treat these symptoms in a rational manner.

Current research is leading to a rapid expansion of our knowledge of the digestive system. This book provides the medical and graduate student with the fundamentals of gastrointestinal (GI) physiology and can serve as a refresher for the medical or surgical resident, and subspecialty fellow. To illustrate the medical relevance of each area of gastrointestinal function, appropriate discussions of pathophysiology and clinical correlations are included. The material in this text is presented using an organ approach, so that the reader can follow a bolus of food down the GI tract and learn physiologic functions of the various organs which the bolus contacts, either directly or indirectly. To minimize repetition of material in subsequent chapters, a brief summary of basic concepts related to the three major functions of the digestive system, that is, motility, absorption, and secretion is presented here.

CONTROL OF GASTROINTESTINAL FUNCTION

The Enteroendocrine System

It is now well recognized that a large number of hormones and related peptides/amines are formed in tissues not generally regarded as part of the classic endocrine system (e.g., hypothalamic-pituitary-adrenal axis). The gut and kidney are examples of such tissues. Indeed, the first hormones to be discovered and so named were of gastrointestinal origin (secretin and gastrin). The endocrine cells of the gastrointestinal mucosa are scattered throughout the epithelium and referred to as "enteroendocrine cells" (EEC). Collectively, they form the largest endocrine system of the body. The peptides/amines produced by the EECs can function as hormones, which are secreted into the circulation to regulate target cells remote from their origin, either 1) within the gastrointestinal system (Table 1-1) or 2) at the level of the central nervous system (CNS), that is, hypothalamus (Table 1-2; the role of these peptides in the regulation of feeding/satiety is addressed in Chapter 2). Some of the listed substances do not behave like classic hormones in that they are released from cells and diffuse through the extracellular space to neighboring target cells. This type of local action is referred to as *paracrine* control.

Most EECs respond to feeding, specifically to the presence of hydrolytic products of food digestion in the lumen (Table 1-1). They act as "chemosensors" coordinating appropriate gastrointestinal responses to ingestion of food. How is a chemical/physical characteristic of luminal contents transduced by the EEC into a functional gastrointestinal response? Most EEC in the mucosa are of the "open type," that is, the microvilli on the apical surface of the cell are in contact with the lumen (Figure 1-2). The microvilli contain receptors for sampling luminal contents, and when these receptors are activated, the EEC discharge the content of their secretory granules into the interstitium. The secreted peptides/amine can then act either as a paracrine or a hormone. Paracrine targets include cells of the epithelium as well as afferent sensory neurons. For example, cytoplasmic protrusions of gastric D cells come in close apposition to G cells, allowing somatostatin to regulate gastrin secretion in a paracrine fashion. The I cells in the duodenal mucosa have basal protrusions that extend toward sensory neurons within the interstitium, facilitating the interaction of CCK with vagal afferents. Endocrine targets are generally located in accessory organs, such as pancreas and liver. Access of a hormone to the bloodstream is facilitated by the close proximity of the blood capillaries and the fact that the capillary fenestrae (pores) always face the basal aspect of the EEC. Some EECs are of the "closed" type that reside entirely in the interstitium and have no connection to the luminal surface. Although closed EEC do not directly respond to luminal contents, they can be regulated

TABLE 1-1: Products of Enteroendocrine Cells (ECC) that Regulate Gastrointestinal Function

EEC	PRODUCT	LOCATION	LUMINAL STIMULUS	PRINCIPAL EFFECT(S)
G cells	**Gastrin**	Stomach	protein hydrolysates, distension	↑ gastric acid secretion
I cells	**CCK***	Proximal Sm intestine	protein & lipid hydrolysates	↑ gall bladder contraction ↑ pancreatic enzyme secretion
S cells	**Secretin***	Proximal Sm intestine	acid	↑ pancreatic & biliary HCO_3- secretion
D cells	Somatostatin*	Stomach & Sm intestine	acid	↓ gastrin release
EC cells	5-HT*, ‡	Entire GIT	toxins, lipid hydrolysates	↑ intestinal motility & fluid secretion
ECL cells	Histamine*	Stomach	closed cell	↑ gastric acid secretion
M cells	**Motilin**	Sm intestine	fasting, nutrients inhibit	↑ migrating motility complex
N cells	Neurotensin	Distal Sm intestine & colon	lipid hydrolysates	↓ gastrointestinal motor activity
K cells	**GIP**	Proximal Sm intestine	carbohydrate & lipid hydrolysates	↑ insulin release
L cells	PYY*, GLP-1	Distal Sm intestine & colon	carbohydrate & lipid hydrolysates	↑insulin release ↓ gastrointestinal motor activity

Products in **bold** are peptides meeting all of the criteria for hormone status. * these products have paracrine actions. ‡ 5-HT can also be found in some I and L cells.

TABLE 1-2: Products of Enteroendocrine Cells (EECs) with Effects on Hypothalamic Feeding/Satiety Centers

CELL	PRODUCT	LOCATION	LUMINAL STIMULUS	PRINCIPAL EFFECTS
I cells	**CCK***	Proximal Sm intestine	lipid & protein hydrolysates	↓ food intake
A/X cells	**Ghrelin***	Stomach	fasting, nutrients inhibit	↑ food intake
P cells	leptin*	Stomach	feeding	↓ food intake
L cells	PYY*, GLP-1	Distal Sm & Lg intestine	lipid & carbohydrate hydrolysates	↓ food intake

Products in **bold** are peptides meeting all of the criteria for hormone status. * these products have paracrine actions.

by paracrine, humoral, and/or neural inputs. For example, gastrin released by G cells can enter the circulation and stimulate enterochromaffin-like (ECL) cells, which reside entirely in the interstitium, to release histamine.

Gastrointestinal Hormones and Related Peptides

To date, there are six peptides generated by the EEC that meet all of the criteria for classification as a hormone (listed in bold in Tables 1-1 and 1-2). Some of the other peptides (e.g., somatostatin, PYY) are referred to as "candidate hormones" and, most likely, will attain full "hormone" status as more information becomes available. Conversely, some of the EEC-derived hormones influence local, rather than remote, target cells. For example, cholecystokinin (CCK)-induced pancreatic enzyme secretion is mediated in part via a neural reflex elicited by the paracrine activation of intramural afferent nerves. As information regarding the function of EEC-derived peptides accumulates, it is becoming apparent that some of these peptides have multiple modes of action, that is, endocrine, paracrine, and/or neurocrine. Thus, the EEC-

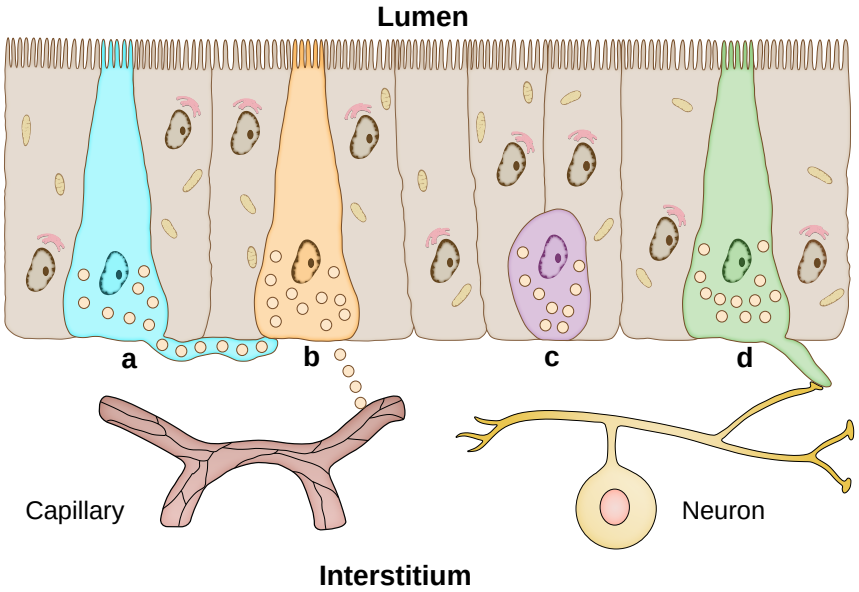

FIGURE 1-2: The enteroendocrine cell (EEC) types of the mucosal epithelium. The EEC labeled as "a, b and d" are of the "open" type, with apical microvilli that can detect and respond to specific luminal contents. "Closed" EEC, labeled "c." do not make contact with the lumen and cannot respond directly to luminal stimuli, instead they are activated by paracrine, endocrine, and/or neural mechanisms. EEC labeled "a and d" have specialized cell extensions that facilitate local, paracrine communication with an adjacent epithelial cell (**a**) or neuron (**d**), respectively. EEC labeled "b" represents a typical endocrine cell whose secreted product enters the circulation to reach its remote target (modified from Gribble FM and Reimann F. *Annu. Rev. Physiol.* 2016; 78: 277-299).

derived peptides are grouped into "families" based on the similarity of their amino acid sequence, rather than their mode of action on target cells.

Cholecystokinin and gastrin are members of the gastrin family. They share an identical sequence of five amino acids (Gly-Trp-Met-Asp-Phe) at the amidated carboxy terminal end of the peptide chain (Figure 1-3). In addition, they are defined by the sulfated tyrosyl residues neighboring the conserved active terminal sequence; position 6 for gastrin and position 7 for CCK. Gastrin and CCK are secreted in different biologically active forms and identified based on the amino acid chain length. The two forms of circulating gastrin are G-17 and G-34. CCK has at least four active forms (CCK-8, CCK-33, CCK-39, and CCK-58). In general, the

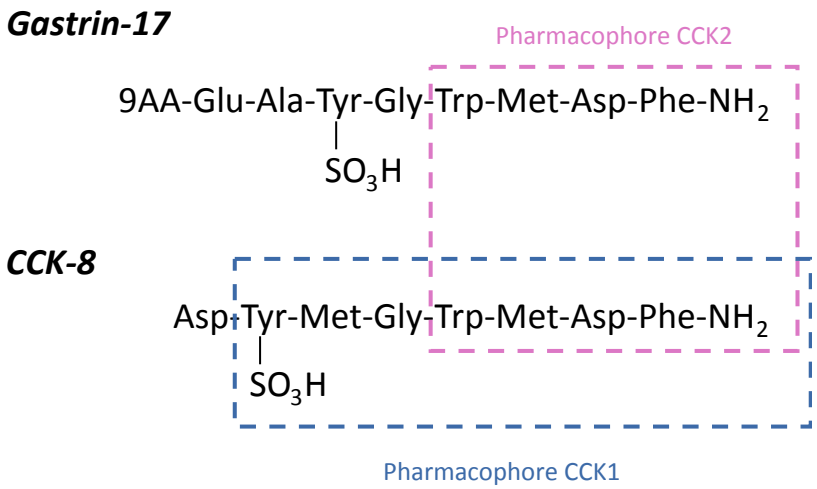

FIGURE 1-3: The amino acid sequences of human gastrin-17 and cholecystokinin-8 (CCK-8) peptides. The pharmacologically active (pharmacophoric) regions recognized by the CCK_1 and CCK_2 receptors are highlighted (from *Pharmacology & Therapeutics* 2008; 119: 83–95. Used with permission of Elsevier).

longer the amino acid chain length the longer the half-life in the circulation. The importance of the carboxy-terminal sequence in the primary structure of both gastrin and CCK is evidenced by the fact that both the synthetic carboxy pentapeptide (pentgastrin) and the carboxy octapeptide of CCK (CCK-8) are active and used clinically.

Because the two hormones share a common sequence of amino acids, they can interact with the same receptor and thus exhibit similar actions. Nonetheless, the relative potency of action of the two hormones differs among target organs. This results from subtle differences in structure and locations of the receptors, known as CCK_1 and CCK_2. Figure 1-3 shows the pharmacophores (molecular structure required for pharmacologic activity) of gastrin and CCK necessary for optimum activation of CCK_1 and CCK_2 receptors. Thus, although CCK can interact with the CCK_1 receptor, gastrin has little affinity for this receptor. Although CCK and gastrin have equal affinity for the CCK_2 receptor, gastrin exerts a dominant influence on the CCK_2 receptor in the gastric mucosa to induce acid secretion, which can be attributed to the 10-fold higher concentration of circulating gastrin (compared to CCK) under physiologic conditions. Ligation of the gastric CCK_2 receptor by CCK can be revealed under conditions of hypogastrinemia (low circulating gastrin). As expected, circulating CCK, but not gastrin,

interacts with CCK_1 receptors in the gall bladder; contracting the bladder wall and propelling bile into the duodenum.

The second group of structurally related peptides, the secretin family, consists of peptides that circulate as single biologically active forms: secretin (27 aa), VIP (28 aa), and GIP (42 aa). Unlike the gastrin family, the structural homologies are internal, that is, identical amino acid sequences exist in segments within the peptide chain. Thus, the functional activity of the members of this family is more dependent on the tertiary, rather than the primary, structure of the peptides. The structural homologies within this group account for some shared spectrum of biologic activities. For example, secretin (a hormone) and VIP (a neurocrine) can stimulate fluid secretion from gastrointestinal organs, such as the duodenum and pancreas. On the other hand, glucose-dependent insulinotropic peptide (GIP) is an incretin (hormone that reduces blood glucose levels) that is secreted from the intestine in response to luminal glucose and stimulates insulin secretion by the pancreas.

Although the gastrin and secretin families of GI hormones are structurally dissimilar, members of one group may potentiate the effect of peptides from the other group in a given target cell. This is explained by the presence of receptors for each family on the same target cell. For example, in pancreatic acini, the interaction of CCK with the CCK_1 receptor leads to an increased intracellular Ca^{++} concentration, whereas the interaction of secretin with its receptor activates the cyclic AMP system (Figure 1-4). Both of these "second messengers" (Ca^{++}, cyclic AMP) work synergistically to promote near optimum enzyme secretion by the cell.

Motilin and ghrelin, the EEC-derived hormones of the ghrelin family, are unique in that they are both released during the interdigestive period (between meals) and inhibited by feeding. Motilin is released from the duodenum and jejunum, whereas ghrelin is produced by the stomach mucosa. Ghrelin is involved in the regulation of food intake by impacting on the feeding/satiety centers in the hypothalamus. Its transport across the blood brain barrier (and biologic activity) is dependent on a unique posttranslational modification, octanoylation (formation of ester with octanoic acid). The only proposed physiologic action of motilin is eliciting the interdigestive motility pattern, the migrating motility complex (MMC).

Intrinsic and Extrinsic Nerves

The gastrointestinal tract is extensively innervated by both the sympathetic and parasympathetic divisions of the autonomic nervous system. Efferent fibers in the vagus (parasympathetic) and

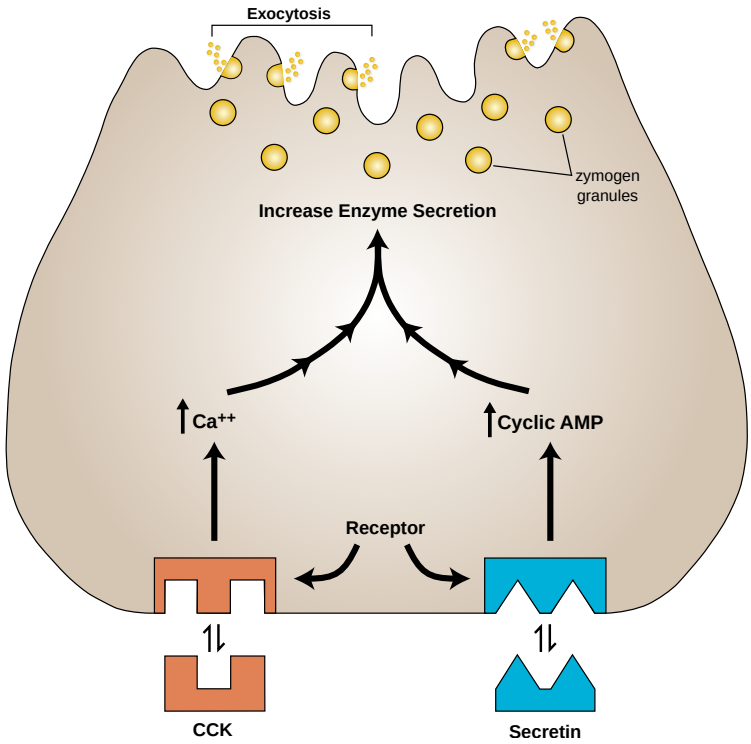

FIGURE 1-4: Mechanisms of action of the GI hormones CCK and secretin in pancreatic acinar cells. The interaction of CCK with its receptor (CCK_1) results in an increased intracellular Ca^{++} concentration, whereas the engagement of secretin with its receptor activates the cyclic AMP system. Both "second messengers" (Ca^{++}, cyclic AMP) work synergistically to promote the exocytosis of zymogen granules and release of pancreatic enzymes.

spinal (sympathetic) nerves allow the CNS to exert an influence on gastrointestinal function. Afferent fibers in these nerves carry information from GI organs to the brain. Furthermore, there is a complex intrinsic nervous system located within the wall of the stomach and gut. The intrinsic nervous system is perceived as an "enteric brain" which can function independently of the CNS to modulate the motor and secretory activities of the stomach and gut.

Intrinsic Innervation

The intrinsic nervous system, also referred to as the enteric nervous system (ENS), consists of two networks of ganglia and fibers located within the wall of the G.I. tract (Figure 1-5).

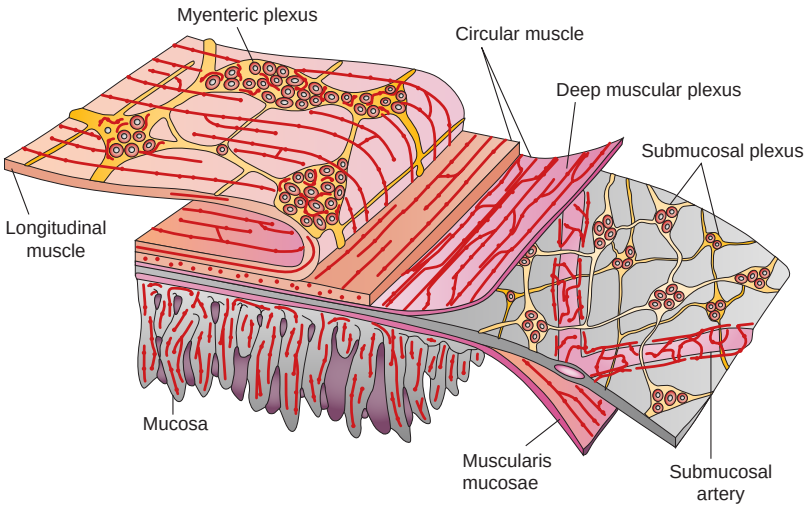

FIGURE 1-5: Organization of the enteric nervous system (ENS). The ENS has two major plexuses: the myenteric plexus, located between the longitudinal and circular muscle layers and the submucosal plexus (SMP). Nerve fibers connect the ganglia and also innervate the longitudinal muscle, circular muscle, muscularis mucosae, arterioles, and mucosal epithelium. **Circles** represent nerve cell bodies in ganglions; **Red lines** represent nerve fibers (modified with permission from *Nat Rev Gastroenterol Hepatol* 2012; 9:286–294, Figure 2, page 288).

One network, the myenteric plexus, is situated between the circular and longitudinal muscle layers and extends from the esophagus to the anal sphincter. The submucosal plexus separates the circular muscle and submucosal layers and is rather sparse or absent in esophagus, but continuous throughout the intestines. Efferent fibers from the myenteric plexus terminate on smooth muscle cells in both the circular and longitudinal layers; therefore, this plexus primarily influences motility (muscle tone and rhythm). The submucosal plexus efferents terminate on the mucosal epithelium (including endocrine cells), on the muscularis mucosa, and, to some extent, on the circular muscle layer. Therefore, this plexus primarily influences epithelial cell activity (e. g., secretion) and to a lesser extent, motor functions. There are many short neurons that link, and allow for communication between, the myenteric and submucosal plexuses.

Numerous transmitters have been identified in the ENS; some of the better characterized are listed in Table 1-3. In the motor neurons of the myenteric plexus, both acetylcholine (Ach) and substance P (SP) have been implicated in contraction of smooth muscles, whereas vasoactive intestinal polypeptide (VIP) and nitric oxide (NO) are considered the major mediators of

TABLE 1-3: Neurotransmitters of the Enteric Nervous System

NEUROTRANSMITTER*	PRINCIPAL EFFECTS
Vasoactive intestinal peptide (VIP)	smooth muscle relaxation ↑ intestinal secretion
Gastrin releasing peptide (GRP)	↑ gastrin release
Substance P (SP)	smooth muscle contraction vasodilation
Nitric oxide (NO)	smooth muscle relaxation vasodilation
Acetylcholine (ACh)	smooth muscle contraction
Calcitonin gene-related peptide (CGRP)	vasodilation

* Neurotransmitters may be co-localized within to a given population of enteric neurons: VIP & nNOS (NO) or ACh & SP.

muscle relaxation. ACh and VIP release from the submucosal plexus have been implicated in the modulation of secretion as well as the vasodilation of submucosal arterioles.

Extrinsic Innervation

Parasympathetics

The parasympathetic nervous system has important secretomotor actions on the entire gastrointestinal tract. The organs of the digestive system are innervated by parasympathetic fibers originating from the medulla oblongata and the sacral part of the spinal cord (Figure 1-6). The medullary outflow comprises the seventh, ninth, and tenth (vagus) cranial nerves. The fibers of the seventh and ninth nerves supply the salivary glands. The vagi supply fibers to the esophagus, stomach, small intestine, proximal part of the large bowel, pancreas, liver, gallbladder, and bile ducts. The sacral parasympathetics originate from the second, third, and fourth sacral segments of the spinal cord and proceed to form the pelvic nerves (*nervi erigentes*). These fibers supply the distal portion of the large bowel, that is, sigmoid, rectum, and anus.

The preganglionic neurons of the parasympathetic supply terminate primarily on the ganglionic cells of the myenteric plexus in the stomach and gut and on the intraparenchymal ganglion cells of the pancreas, salivary glands, and liver. The preganglionic neurotransmitter is

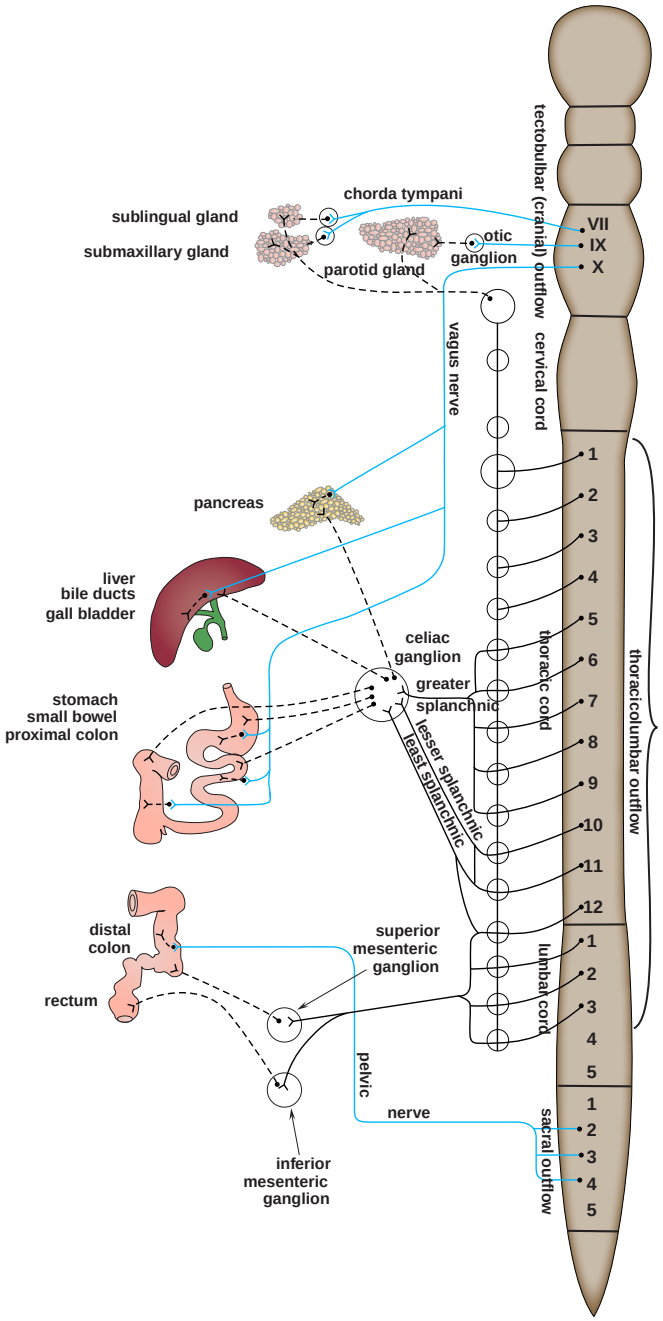

FIGURE 1-6: Extrinsic parasympathetic (blue lines) and sympathetic (black lines) innervation of the digestive system. Solid lines represent preganglionic fibers and broken lines represent postganglionic fibers (modified from Goodman, L.S. and Gilman, A. The Pharmacologic Basis of Therapeutics, 12th Edition, with permission of McGraw-Hill Professional).

acetylcholine, which interacts with *nicotinic* receptors on the postsynaptic membrane of ganglion cells. Acetylcholine also serves as a neurotransmitter at postganglionic nerve terminals, where it interacts with *muscarinic* receptors on effector cells (e.g., acinar cell of pancreas). A large number of other postganglionic neurotransmitters (or neurocrines) have been identified within the ENS of the stomach and gut that can exert either excitatory or inhibitory effects on GI function; some of the well-characterized neurocrines are listed in Table 1-3.

Sympathetics

Unlike the parasympathetic supply to the GI tract, which originates from the cranial and sacral segments of the cord, the sympathetic supply stems from the midportion of the cord, that is, the thoracic and lumbar segments (Figure 1-6). The preganglionic fibers enter the sympathetic chains after leaving the cord. The postganglionic fibers that terminate on the salivary glands arise directly from the superior cervical ganglia, which are located within the chains. All other digestive organs receive postganglionic fibers originating from outlying ganglia, such as the celiac, superior mesenteric, and inferior mesenteric ganglia, which in turn receive preganglionic fibers from the sympathetic chain. The celiac ganglia supply fibers to the esophagus, stomach, proximal duodenum, liver, and pancreas; the superior mesenteric ganglia supply fibers to the remainder of the small bowel and proximal colon; and the inferior mesenteric ganglia supply fibers to the distal colon and rectum. Some fibers make synaptic connections with the intrinsic nerve plexuses of the stomach and gut, whereas others end directly on blood vessels and, to a lesser extent, on other parenchymal structures. Synaptic transmission between preganglionic and postganglionic fibers of the sympathetic nervous system involves acetylcholine, whereas the postganglionic neurotransmitter is norepinephrine.

Afferent Nerve Fibers

Afferent fibers from the GI tract also travel in autonomic nerves (Figure 1-7). For example, 80% of vagal fibers and 50% of the sympathetic fibers are afferent. All of these fibers transmit sensory information to the central nervous system. Some of this information reach the conscious level, chiefly in the form of pain, whereas other information are a component of vegetative reflex arcs controlling GI function. Sensations of pain emanating from noxious stimuli in the GI tract are carried in spinal afferent fibers whose cell bodies are located in the dorsal root ganglia (DRG). Vagal afferent fibers involved in homeostatic regulation of GI functions (e.g., motility, secretion, satiety) have their cell bodies in the nodose ganglion (NG). In general, their

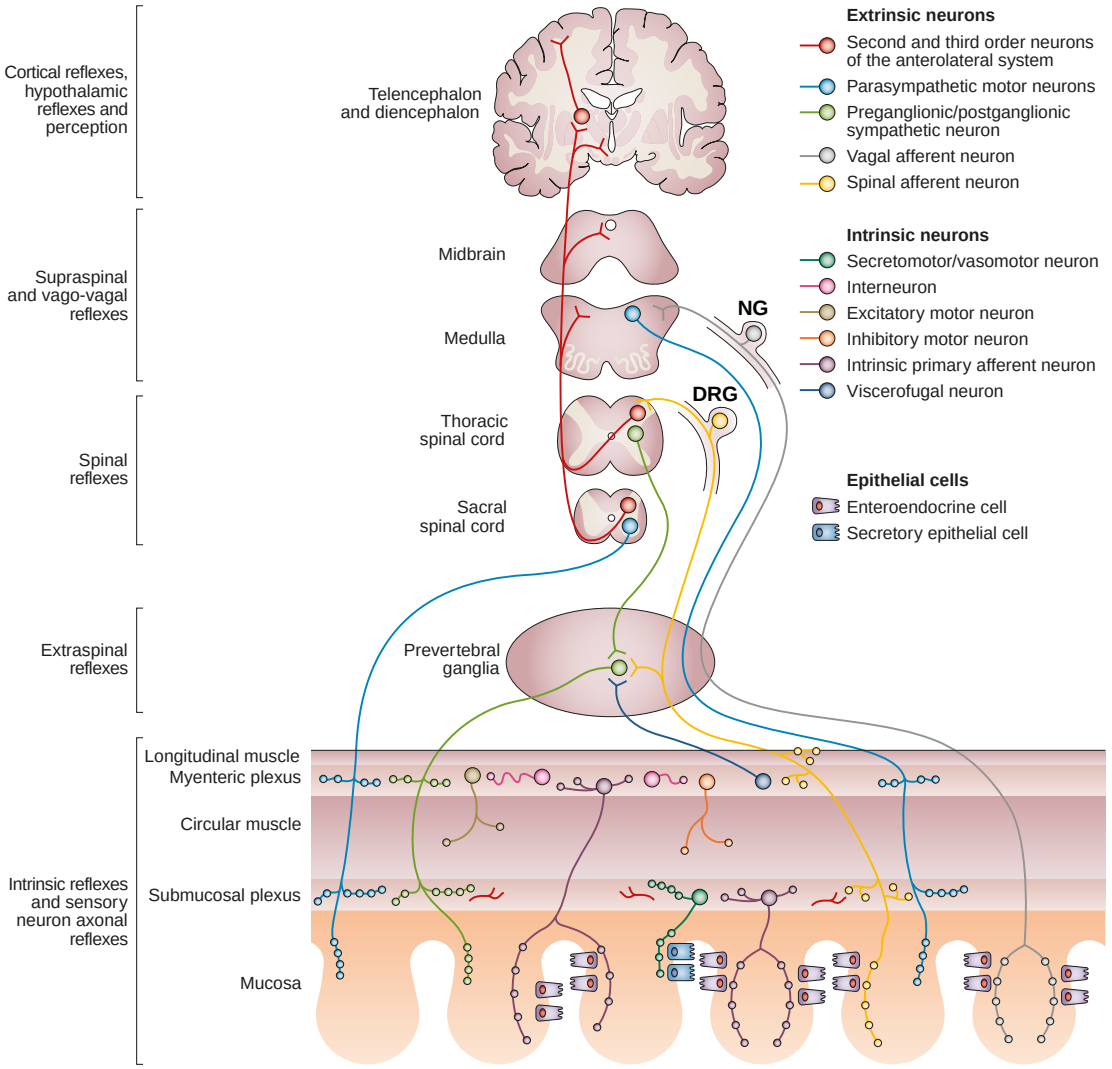

FIGURE 1-7: Multiple levels of reflex control of gastrointestinal function. Sensations of pain emanating from noxious stimuli in the GI tract are carried in spinal afferent fibers whose cell bodies are located in the dorsal root ganglia (DRG). Vagal afferent fibers involved in homeostatic regulation of GI functions (e.g., motility, secretion, satiety) have their cell bodies in the nodose ganglion (NG). Their efferent fibers impact on gastrointestinal smooth muscle, epithelial cells and blood vessels to complete various reflex arcs (reprinted with permission from *Nat Rev Gastroenterol Hepatol* 2014; 11: 611–627).

receptive fields and terminals are located in either the vicinity of the mucosa or muscularis to either receive chemical/irritant or distension/stretch input, respectively. Their efferent fibers impact on gastrointestinal smooth muscle, epithelial cells and blood vessels to complete various reflex arcs. These reflexes are generally referred to as "long reflexes" because they involve a response at a remote site from the initiating stimulus. Their specificity is denoted by a term combining the afferent and efferent components of the reflex arc. For example, the "enterogastric reflex" is initiated by activation of sensory afferents in the duodenum in response to mucosal irritation and terminates via vagal efferent fibers in the stomach to inhibit gastric emptying. Thus, the enterogastric reflex is a mechanism by which the intestine can regulate the delivery of gastric contents to its lumen.

There are also intrinsic sensory afferents whose cell bodies and effector arms are located within the wall of the gastrointestinal tract (Figure 1-6). By contrast to the extrinsic sensory afferents, the intrinsic afferent neurons do not transmit sensory information to the brain. Instead, they initiate reflexes through an interconnected series of neural networks to regulate motility, secretion, and blood flow. These reflex arcs are referred to as "short reflexes," because the reflex arc is usually confined to very short segments. For example, the "peristaltic reflex" is initiated by the presence of a bolus of chyme (ingested food) in the intestinal lumen. The intrinsic neurons initiate a local constriction of circular muscle proximal to the bolus and a relaxation distally, thereby propelling chyme aborally for only a few centimeters. The peristaltic reflex can be elicited even after severing all autonomic nerves (parasympathetic and sympathetic) and is sometimes referred to as an "intrinsic reflex."

Sensory Transduction

The mechanisms involved in sensory transduction in the extrinsic and intrinsic afferents is dependent on the stimulus. Distention/stretch of the musculature or mucosal deformation activates mechanoreceptors on afferent extrinsic or intrinsic neurons, respectively. It has been proposed that local afferents detecting mucosal deformation may monitor the movement of chyme over the mucosal surface. Moderate distension can elicit physiologic reflexes in the upper and lower gastrointestinal tract. Gastric distension can give rise to a sensation of "fullness" and impact food intake. Rectal distension usually results in the urge to defecate. Excessive distension, however, can elicit discomfort and pain, a nociceptor reflex probably mediated via the spinal afferents and dorsal root ganglion. In a similar manner, the presence of noxious stimuli (e.g., acid, bacterial toxins) in the gastric and/or intestinal lumen can result in activation of afferent sensory neurons

and pain perception. However, because the afferent sensory fibers do not extend into the lumen (Figure 1-7), this latter function of sensory afferents depends on the noxious stimuli reaching the nerve terminals via transport across (or breech of) the epithelial lining.

The chemosensing of both innocuous (e.g., nutrients) and noxious (e.g., bacterial toxins) agents has been relegated to the various EEC of the mucosal epithelial lining. As mentioned above, the EEC can sample luminal contents and release a variety of mediators, some of which can activate adjacent sensory afferent neurons in the subepithelial space. The enterochromaffin cells (EC) are the most numerous of the EEC and their product serotonin (or 5-hydroxytryptamine; 5-HT) has received much attention as a primary chemosensory transducer. Serotonin has been implicated as a mediator in various GI functional activities, including motility, secretion, even the sensations of nausea and pain. For example, enterochromaffin cells detect the presence of chyme in the lumen and release serotonin, which initiates reflex intestinal contractions. Furthermore, the EC can detect bacterial toxins (e.g., *V. cholera* enterotoxin) and serotonin initiates the appropriate reflex secretory and motor activity to dilute and wash away the toxin. Negative feedback regulation of these responses is accomplished by uptake of serotonin by epithelial cells; most of which express the serotonin-selective reuptake transporter (SERT).

Other EEC have been implicated as chemosensory transducers in reflex responses of the gastrointestinal tract to nutrients in the lumen. The classic hormones CCK and secretin are now believed to exert at least some of their effects via activation of sensory afferent neurons. For example, the enterogastric reflex, which is initiated by irritants in the duodenal lumen, is likely mediated by CCK activation of afferent sensory neurons via the CCK_1 receptor. This is not entirely surprising considering that one of the major irritants initiating the reflex are long chain fatty acids, which are also the major stimuli for activating I cells (CCK-producing EEC in duodenum) to secrete CCK. The peptides released by EEC that have been implicated in feeding and satiety also appear to exert their effects, at least in part, via activation of sensory afferents (Table 1-2).

GASTROINTESTINAL FUNCTIONS

Motility

Efficient assimilation of nutrients by the gastrointestinal tract depends on an orderly intraluminal flow of ingested food at a rate that allows for optimum digestive and absorptive activity. Propulsion of food is accomplished by the coordinated motor activity of the gut; a function attributed to its smooth muscle coat. Motility is concerned not only with propulsive activity but also with the

mixing of foodstuff with digestive secretions. One important digestive secretion, bile, is delivered into the lumen of the gut by contraction of the smooth muscle lining the gallbladder.

The smooth muscle coat of the gut is characteristically arranged in two layers, an inner circular and an outer longitudinal (Figure 1-5). In addition, a thin layer of smooth muscle (the muscularis mucosa), which may mediate mucosal (villus) motion, separates the mucosa from the submucosa. At the upper end of the gastrointestinal tract, striated muscle is found in the oropharynx and upper one third of the esophagus, and this striated muscle blends with the smooth muscle of the mid-esophagus. The remainder of the gastrointestinal tract is composed of smooth muscle except for the external anal sphincter, which consists of striated muscle. At various strategic points along the alimentary tract, specialized areas of smooth muscle serve to regulate the movement of chyme and secretions between adjacent luminal compartments (e.g., stomach and duodenum). The term sphincter is applied to these regions, some of which are characterized by a thickened band of circular smooth muscle, for example, the upper esophageal sphincter, the pylorus, and the sphincter of Oddi. Others are functional sphincters with no specialized structural features that, nonetheless, generate a zone of high intraluminal pressure. An example of these functional sphincters is the lower esophageal sphincter.

Basal Electrical Rhythm and Interstitial Cells of Cajal

Gastrointestinal smooth muscle is characterized by a resting membrane potential which can depolarize to initiate contraction. The resting membrane potential of gastrointestinal smooth muscle ranges from –55 mv to –80 mv, with a mean of about –60 mv. This potential is created by the distribution of Na^+, K^+, and Cl^- ions across the cell membrane. In contrast to most other excitable tissues, where the resting membrane potential remains fairly constant, the resting potential of gastrointestinal smooth muscle is characterized by rhythmic fluctuations (Figure 1-8). The oscillations of the potential have an amplitude of 15 to 20 mv, a duration of 1 to 5 seconds, and a frequency which varies along the gut, that is, 3/min in the stomach, 12/min in the duodenum, declining progressively to 8/min in the ileum. These rhythmic depolarizations are called slow waves or the *basal electrical rhythm* (BER).

Although isolated GI smooth muscle cells do not exhibit spontaneous depolarizations (slow waves), adjacent interstitial cells of Cajal (ICC) do. It is widely held that ICC act as "pacemakers" that elicit slow waves in smooth muscle. The oscillating slow waves generated in the ICC networks are transmitted across gap junctions to smooth muscle cells, which results in the BER. Within the GI tract, ICC are distributed in networks that lie in close proximity to the neural plexuses found within and between the muscle layers (Figure 1-9). These networks allow

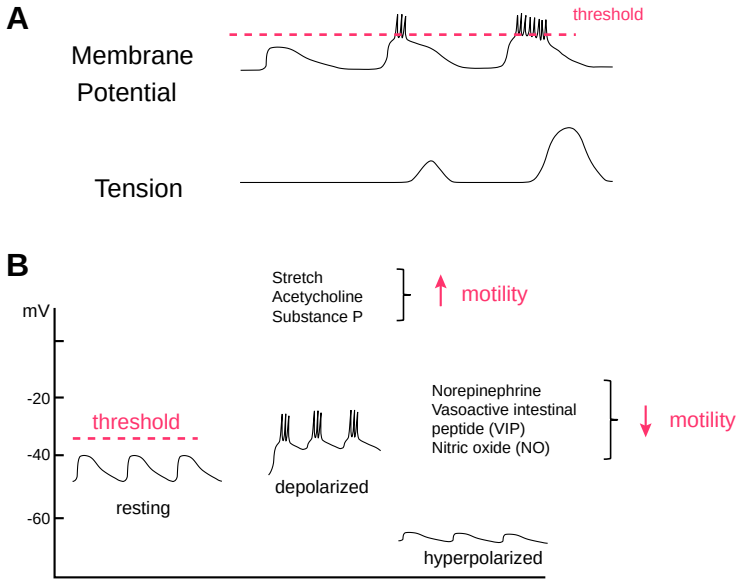

FIGURE 1-8: Relationships among slow waves, action potentials and contractile activity of intestinal smooth muscle. **A**. Slow waves are rhythmic cycles of membrane potential depolarizations and when a threshold potential is reached action potentials are generated. Smooth muscle contraction (increased tension) occurs only when action potentials are present on the slow waves; the strength of contraction is directly related to the number of action potentials. **B**. Stimuli either depolarize the membrane potential toward the threshold for generation of action potentials and increase smooth muscle contractile activity (motility) or hyperpolarize the membrane potential and inhibit motility.

for electrical coupling of the ICC with one another and with adjacent smooth muscle cells. For example, the ICC within the myenteric region (ICC-MY) are believed to function as the pacemakers that generate and transmit the slow waves in adjacent smooth muscle cells. The ICC network in the region of the deep muscular plexus (ICC-DMP) is in close apposition to nerve varicosities and is believed to play an important role in the transmission of nerve impulses to the smooth muscle.

Excitation-Contraction Coupling

Superimposed on the depolarization phase of the slow wave are small generator potentials, which, when they reach a critical threshold voltage, give rise to a spike or action potential (Figure 1-8). These spikes are responsible for initiating muscle contraction, the strength of which

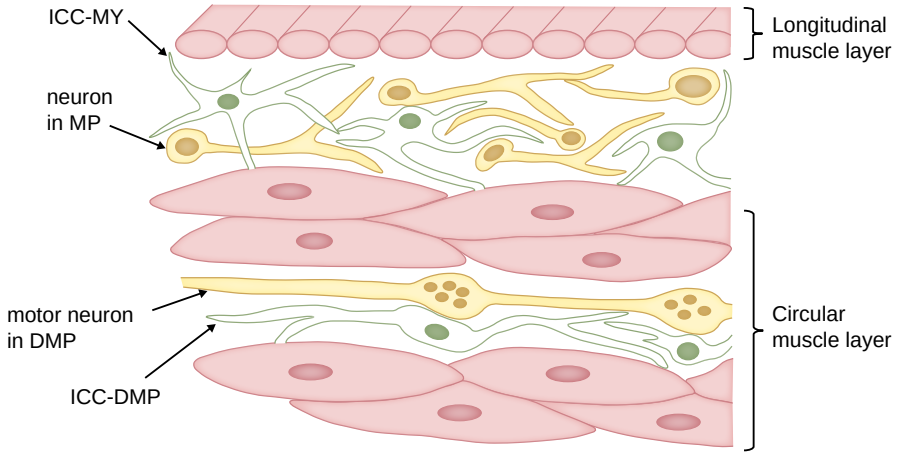

FIGURE 1-9: Interstitial cells of Cajal (ICC) between and within muscle layers of the intestine. Myenteric ICC (ICC-MY) are located in the region of the myenteric plexus (MP), between the circular and longitudinal muscle layers. This ICC network is responsible for generating the pacemaker slow waves that are transmitted to the smooth muscle cells. Intramuscular ICC (ICC-DMP) are located in the region of the deep muscular plexus (DMP) within the circular smooth muscle in close proximity to varicosities of motor neurons. This ICC network appears to relay neural information to smooth muscle cells and act as mechanosensors (adapted from Sanders KM, Kito Y, Hwang SJ, Ward SM. *Physiology* 31: 316–326, 2016).

is determined by the number of spikes generated (Figure 1-8A). The pre-potential and action potential involve an influx of Na^+ and Ca^{++} into the smooth muscle cell, owing to changes in membrane conductance for these ions. The Ca^{++} entering the cell is involved in the initiation of smooth muscle contraction. Stimuli that enhance motility result in smooth muscle depolarization (e.g., stretch, acetylcholine, substance P) and raise the membrane potential to the threshold for the generation of spike potentials, whereas factors that reduce motility (e.g., norepinephrine, VIP, nitric oxide) typically hyperpolarize the muscle and move the membrane potential further below the threshold potential (Figure 1-8B). This leads to a reduction in intracellular calcium and subsequent muscle relaxation.

The contractile activity of smooth muscle can be compared with and contrasted with that of striated muscle. Smooth muscle cells are much smaller and have a greater surface-to-volume ratio than skeletal muscle cells. Although both muscle types contain similar contractile proteins (actin and myosin filaments) that require Ca^{++} for activation, the excitation-contraction coupling is somewhat different in smooth and striated muscle cells. The rise in intracellular

Ca^{++} in smooth muscle is primarily a result of an influx of extracellular Ca^{++}, whereas mobilization of intracellular stores is more important in striated muscle. The high surface-to-volume ratio in smooth muscle cells facilitates the influx and intracellular diffusion of calcium. Smooth muscle cells also lack troponin, which is present in skeletal muscle cells. Therefore, Ca^{++} initiates smooth muscle contraction via calmodulin-mediated activation of myosin filaments. As in striated muscle, the energy for contraction is derived from degradation of adenosine triphosphate (ATP).

Smooth muscle contraction does not begin until 50 to 100 milliseconds after excitation and requires an additional 500 milliseconds for development of maximum tension. The entire cycle requires 1 to 3 seconds and is 30 times longer than a single twitch contraction of skeletal muscle. The latency to onset of contraction is due to the time required for Ca^{++} to enter and diffuse throughout the cell. The slow relaxation depends on the removal of Ca^{++} by intracellular depots.

How is electrical and contractile activity propagated longitudinally and perpendicularly in the two layers of the gastrointestinal tract? A fundamental feature of smooth muscle cells is the presence of *gap junctions* or *nexi*, which confer the properties of a functional syncytium. These gap junctions provide a low resistance pathway for the movement of ions and thereby facilitate electrical conduction from cell to cell. In addition, there is a prominent role for ICC in the propagation of electrical/contractile activity. ICC connections allow for propagation of electrical activity within the network and the connections of ICC to smooth muscle cells within the circular and longitudinal muscle layers elicits the activation of these cells. It is generally held that the coordinated mixing and propulsive contractile activity of the GI tract is dependent on a functional syncytium composed of both smooth muscle and ICC.

Contractile activity of the gastrointestinal tract is regulated by both extrinsic and intrinsic neural influences on the basal electrical rhythm (Figure 1-7B). For example, the postganglionic parasympathetic (vagus) neurotransmitter, acetylcholine, reduces the overall membrane potential while preserving the basal electrical rhythm, thereby increasing the tendency for spike discharge and contractile activity. Norepinephrine, on the other hand, tends to hyperpolarize or stabilize the membrane against other agents that cause depolarization. In general, sympathetic discharge tends to reduce gastrointestinal motor activity, whereas parasympathetic discharge enhances it. The myenteric plexus also contains both excitatory and inhibitory neurons that regulate motility in a manner similar to the autonomic nerves (Table 1-3). Excitatory neurons induce local contractions via neurotransmitters that elevate (depolarize) the membrane potential (e.g., acetylcholine, substance P). Inhibitory neurons produce local relaxations via neurotransmitters (e.g., VIP or NO) that lower (hyperpolarize) the membrane potential.

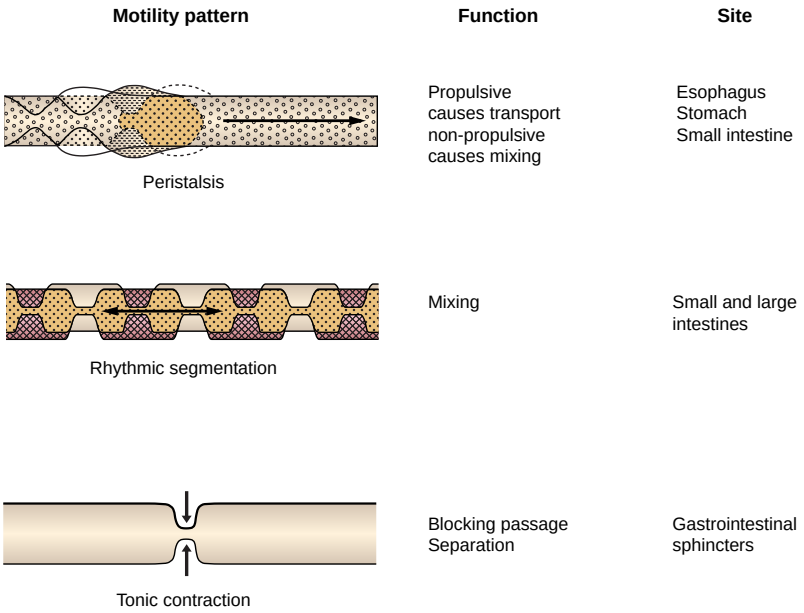

FIGURE 1-10: The three major patterns of GI motility. Peristalsis involves a local reflex that is elicited when the gut wall is stimulated by a food bolus. Peristaltic contractions consist of a wave of circular muscle contraction that is elicited upstream from the food bolus and a wave of relaxation in the adjacent downstream section of the bowel. Rhythmic segmentation involves alternating contractions and relaxations at different sites along the bowel, which function to mix ingested nutrients with digestive secretions. Tonic contraction, with intermittent relaxation, of the sphincters serves to regulate movement of luminal contents along (and secretions into) the GI tract.

Functional Motor Patterns

Electrical and contractile events in gastrointestinal smooth muscle lead to three major patterns of motility: rhythmic segmentation, peristalsis, and tonic contractions (Figure 1-10). Rhythmic segmentation, which is attributed to the activity of the circular muscle layer, mixes ingested nutrients with digestive secretions. In addition, segmentation tends to move intestinal contents anal-ward (downstream), because the frequency of these segmental contractions is higher in the upper than lower small intestine. Another factor that contributes to the forward propulsion of luminal content along the gastrointestinal tract is peristaltic activity. Peristalsis involves a local reflex mediated through the myenteric plexus that is elicited when the gut wall is stimulated by a food bolus. Peristaltic contractions consist of a wave of circular muscle contraction that is

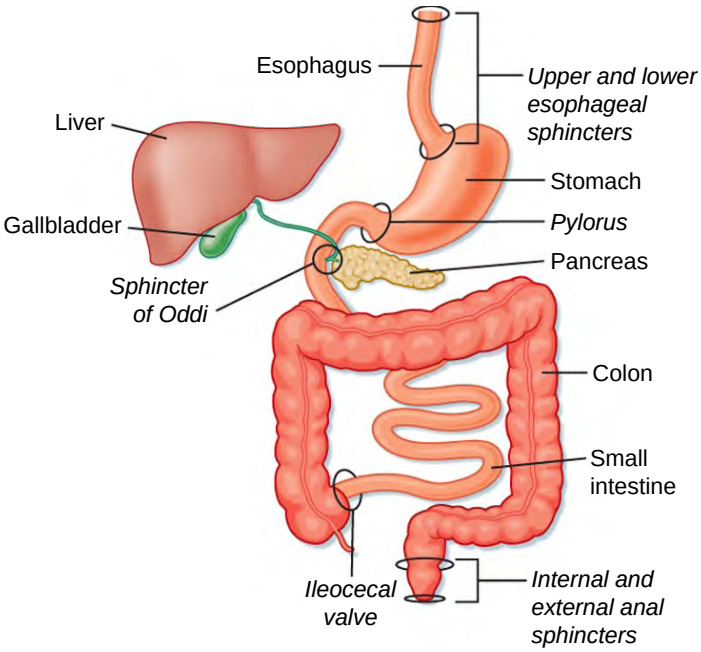

FIGURE 1-11: Sphincters control the flow of food/chyme within, as well as the movement of digestive secretions into, the GI tract. These areas of smooth muscle resistance include the upper and lower esophageal sphincters, pylorus, sphincter of Oddi, ileocecal valve, and the internal and external anal sphincters (modified with permission from Berne and Levi Physiology, 6th edition, 2008, Mosby, with permission of Elsevier).

elicited upstream from the food bolus via activation of excitatory neurons that release acetylcholine and substance P. The contractile wave is coupled to a wave of relaxation in the adjacent downstream section of the bowel that results from the reflex-mediated activation of inhibitory neurons that release nitric oxide and VIP. Although peristalsis can be conducted in both directions, the reflex relaxation confers the observed polarity of peristaltic activity, that is, movement in the oral to anal direction.

Tonic contraction, with intermittent relaxation, of the sphincters serves to regulate 1) movement of luminal contents along the gastrointestinal tract and 2) delivery of digestive secretions from the pancreas and liver. The upper esophageal and external anal sphincters are under somatic control, whereas the others are under control of the autonomic nervous system. The sphincters compartmentalize the different functional regions of the GI tract (Figure 1-11). For example, the lower esophageal and pyloric sphincters isolate the acid-producing stomach from

adjacent esophageal and intestinal compartments, where acid-induced injury could result. These sphincters open intermittently to allow for the passage of ingested material to the next compartment. The sphincter of Oddi regulates the delivery of pancreatic enzymes and biliary secretions to coincide with the presence of ingested nutrients in the intestine to facilitate digestion/absorption. The ilealocecal valve serves to prevent the colonic microbiota from entering the intestine, where the bacteria can result in maldigestion/malabsorption of nutrients and even toxicity.

Digestion

The human diet consists largely of carbohydrate, protein, and fat derived from animal and vegetable sources. These chemically complex substances are reduced to smaller absorbable units by digestive enzymes. The sources of intraluminal digestive enzymes are the digestive glands, some of which are located in the GI tract itself (e.g., gastric glands), whereas others lie outside the GI tract (pancreas and salivary glands) and deliver their secretions to the gut lumen through ducts.

Digestive enzymes are proteins that are synthesized, stored, and secreted by specialized cells found in salivary glands, stomach, pancreas, and intestines. The secretion of proteins (i.e., enzymes) is an orderly process, beginning with synthesis of the peptide chain in the basal portion of the cell and culminating with extrusion of the proteins at the apical region. The secretory cycle can be divided into the following six intracellular events: synthesis, segregation, intracellular transport, concentration, storage, and discharge. The enzymes are synthesized by polysomes attached to the rough endoplasmic reticulum, and the elongating peptide chain is directed into the cavity (cisterna) of the endoplasmic reticulum. This form of synthesis effectively segregates the secretory proteins to a membrane-bound compartment, which assures appropriate channeling of the protein through a series of subcellular organelles to their ultimate site of secretion. The newly synthesized proteins move through the cisternae to "transitional elements" of the rough endoplasmic reticulum that are subsequently pinched off and transport the proteins to the concentrating vacuoles of the Golgi apparatus. Within these vacuoles, the nascent proteins are concentrated to produce mature storage granules (zymogen granules). After their formation in the Golgi complex, the secretory granules migrate to the apical portion of the cell and remain there until an appropriate stimulus (neural or humoral) triggers exocytosis (Figure 1-4). Exocytosis involves the orderly movement of the granule toward the apical cell membrane and fusion of the zymogen granule and cell membrane. Then, the membranes dissolve at the point of fusion, releasing the granule contents from the cell.

The digestive enzymes hydrolyze ingested carbohydrates, lipids, and proteins by attacking glycosidic, ester, and peptide bonds, respectively. Under physiologic conditions, the pancreatic enzymes are the most important and the small intestine the primary site of hydrolysis. Hydrolysis can occur within the gut lumen, at the apical membrane of the absorptive cell, or within the cytoplasm of this cell, depending on the nutrient and location of the digestive enzymes. Intraluminal hydrolysis, the initial digestive event, is accomplished primarily by enzymes secreted by the glands associated with the gastrointestinal tract, of which the pancreas is the most important. In general, all three classes of nutrients undergo preliminary hydrolysis in the lumen for effective absorption to occur. In the case of fat, this digestive step is facilitated by biliary secretions and yields monoglycerides and fatty acids, both of which are lipid soluble and thus require no further modification before absorption. Carbohydrates and proteins, on the other hand, undergo further processing. The complex glucose polymers (starch and glycogen) are hydrolyzed in the lumen to a mixture of monosaccharide and oligosaccharides (up to 4 to 5 glucose units). Because carbohydrates can only be absorbed as monosaccharides, the oligosaccharides are further hydrolyzed to yield glucose moieties by saccharidases located in the apical membrane of mucosal cells. Intraluminal hydrolysis of proteins also yields a mixture of smaller fragments consisting of amino acids and peptides of various sizes. Because only amino acids and small peptides (dipeptides and tripeptides) can be transported into enterocytes, larger peptides are further processed to a transportable size by peptidases in the microvilli. Intracellular dipeptides and tripeptides are further hydrolyzed to yield amino acids for final transport to the interstitium and blood stream.

Absorption

Absorption in the gastrointestinal tract involves the uptake of a heterogeneous group of substances (water, electrolytes, and nutrients) from an aqueous medium. These substances vary in several important aspects that determine their mode of absorption. Molecular size, charge (or lack thereof), and relative aqueous and lipid solubilities are major influences in this regard.

Routes of Absorption

The major site of absorption of the hydrolytic products of food digestion, electrolytes, and water is the small intestine. Solutes encounter various barriers and channels during their transit from the bulk aqueous phase of luminal content to the blood and lymphatic circulations. The first barrier is a mucus layer adherent to the luminal surface of the epithelium which can act as a sieve restricting molecules based on size and lipophilicity. The size restrictions of this mucus

gel, although inhibiting indigestible particulate matter and pathogens, does not significantly hinder the passage of the small hydrophilic products of nutrient digestion. However, lipophilic solutes would be hindered significantly due to hydrophobic interactions with mucins. The mucus layer of the small intestine is estimated to be approximately 15 to 30 μm thick; the layer is thinnest or even absent in the upper small intestine (major site of absorption). Taken together, the physical and chemical characteristics of the adherent mucus gel do not present a substantially greater barrier to the absorption of nutrients than an unstirred water layer of similar thickness.

The next barrier to solute movement is the cell membrane and its associated structures. The cell membrane, a lipid bilayer containing phospholipids and cholesterol, has a mosaic pattern of proteins and glycoproteins associated with it. The proteins of the cell membrane can be classified as either integral or peripheral. Integral proteins are embedded in the phospholipid bilayer, bridging it from its extracellular to intracellular surface. The peripheral proteins are attached to either surface and are believed to subserve primarily enzymatic and signaling functions. The integral proteins behave as enzymes or carriers and provide structural channels through the lipid membrane. The large surface area offered by the exposed lipid portion of the membrane allows for easy passive transit of lipid-soluble molecules into the cell, regardless of their size. For water and water-soluble molecules, the lipid membrane provides a more formidable barrier to entry into the cell; consequently, they rely on the structural proteins to traverse the cell membrane. Aqueous channels formed by the integral proteins provide a route of access to the cell interior for small water-soluble substances (e.g., electrolytes) as well as water. The dimensions of these channels (or pores) in gastrointestinal epithelia average about 8 Å in diameter, with larger pores in the duodenum than in the ileum. Because these channels are created by charged proteins, electrolyte movement through them may be either facilitated or hindered, depending on the ion species and the pore charge. For example, the epithelium of the gallbladder has an excess of negatively charged pores, whereas in the stomach, cationic pores predominate. Some channels, called aquaporins, selectively conduct water molecules in and out of the cell, while preventing the passage of ions and other solutes.

Another route by which electrolytes and water cross the mucosal epithelia is the tight junctions that connect adjacent absorptive cells. These paracellular or intercellular channels (Figure 1-10) behave as if they have different degrees of porosity in different tissues. For example, much more fluid and electrolytes cross the intercellular junctions of the gallbladder epithelium than cross the intestinal epithelium.

Neither the tight junctions nor the protein channels of the cell membrane offer suitable routes for the absorption of large water-soluble nutrients such as glucose and amino ac-

ids. For the uptake of these substances, mechanisms exist that involve specialized "carrier" proteins. These proteins can "shuttle" molecules across the cell membrane. For large molecules, the possibility also exists that pinocytosis may account for cellular uptake from the intestinal lumen.

The remaining barriers in the absorptive process are the basolateral membrane of the enterocyte, its basement membrane, the interstitium of the lamina propria, and the endothelial cell wall of capillaries and lymphatics. Relatively little is known about these barriers. Located in the basolateral cell membrane are energy-dependent ion pumps that promote the exit of electrolytes and water. Larger water-soluble molecules, such as monosaccharides and amino acids, cross the basal membrane by facilitated diffusion using carrier proteins. Chylomicrons (750 to 6000 Å diameter), which are formed in the cell during fat absorption, leave by exocytosis through the basolateral cell membrane. The lateral intercellular space between enterocytes is the final common pathway for a heterogeneous collection of water, solutes, and lipid particles which then cross the basement membrane, traverse the interstitium, and reach the blood and lymphatic circulations. The water-soluble substances enter blood capillaries and chylomicrons enter the initial lymphatics.

Mechanisms of Absorption

Substances are primarily absorbed by two basic processes, diffusion and active transport. Diffusion can be defined as the movement of molecules along an electrical (difference in charge) or chemical (difference in concentration) gradient or both (electrochemical). Diffusion is a passive process governed by simple physical laws and requires no energy input. Active transport, on the other hand, involves the movement of molecules uphill against a concentration, electrical, or pressure gradient and therefore requires energy.

Passive Absorption Lipid-soluble substances cross the lipid portion of the cell membrane in accordance with their concentration gradients. Water-soluble substances can also enter the cell by passive diffusion. Small solutes (electrolytes), whose dimensions are smaller than the aqueous pores, can diffuse through these channels. Larger water-soluble molecules are obliged to use an alternative route involving carrier proteins in the membrane (Figure 1-12). The molecule to be transported, such as the monosaccharide fructose, couples with its carrier on the external side of the membrane and the complex either diffuses or rotates within the membrane. At the inner face of the membrane, the transported molecule dissociates from its carrier. This carrier is analogous to the aqueous pores in that the laws governing simple diffusion still operate,

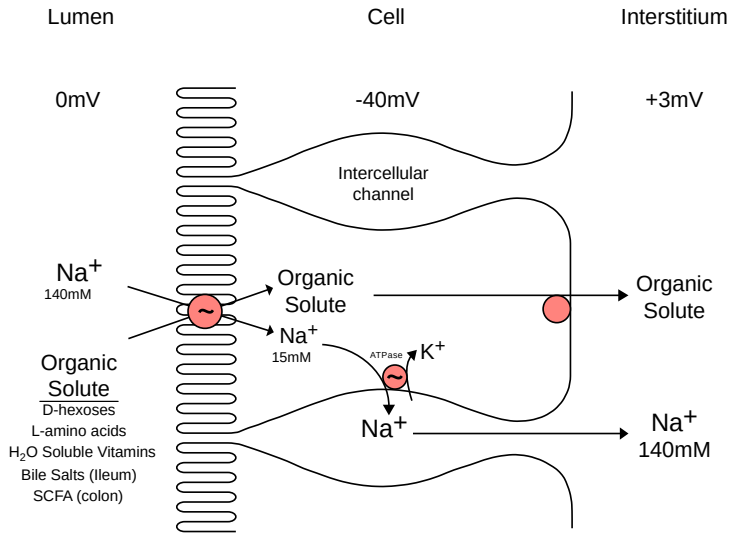

FIGURE 1-12: Secondary, or electrolyte-coupled transport, is used by intestinal epithelial cells to absorb monosaccharides, amino acids, and other water-soluble organic solutes. A Na^+-solute (e.g., glucose) carrier protein on the brush border membrane has binding sites for both Na^+ and the organic solute. Both molecules move into the enterocyte by facilitated diffusion down Na+ concentration (140 → 15 mM) and electrical (0 → –40 mv) gradients created by the energy-dependent Na^+-K^+ pump located in the basolateral membrane.

and this process is termed *facilitated diffusion*. However, an important difference exists between simple diffusion and facilitated diffusion. Because facilitated diffusion depends on a fixed number of carrier protein sites, this process is saturable, unlike simple diffusion.

Active Absorption Water-soluble substances can also be actively transported across the cell membrane. Actively transported substances include ions such as Na^+, K^+, Cl^-, H^+, Ca^{++}, and Fe^{++}, as well as certain monosaccharides, amino acids, and peptides. Active transport processes can be divided into two main types, primary (ATP-coupled) and secondary (electrolyte-coupled).

An example of a primary active transport process is the exchange of Na^+ and K^+ across the cell membrane as illustrated in Figure 1-12. The active transport of Na^+ and K^+ is a characteristic of all cells in the body and is responsible for the extracellular and intracellular distribution of these ions. Both ions are moved against their concentration gradients by means of a carrier protein possessing enzymatic activity (Na^+, K^+-ATPase). The enzymatic activity of this

carrier provides the energy required for transport by virtue of its intrinsic ability to hydrolyze ATP. The hydrolysis of ATP occurs on the inner portion of the membrane, and the energy so derived enables the carrier to transport sodium out of the cell and potassium into the cell. The transport of these ions is coupled in such a manner that three Na^+ ions are extruded from the cell for every two K^+ ions taken in. In the absorptive epithelia of both the intestines and gallbladder, the Na^+-K^+ pump is located in the basolateral portion of the cells.

Secondary, or electrolyte-coupled transport, is a very important mechanism for the active absorption of monosaccharides, amino acids, and peptides. An example of electrolyte-coupled transport is the absorption of glucose by the enterocyte (Figure 1-12). As mentioned above, the sodium-potassium pump is located in the basolateral portion of the epithelial cell, and by depleting intracellular sodium, it creates a favorable electrochemical gradient for the diffusion of Na^+ from the lumen into the mucosal cell. The apical portion of the cell membrane contains a Na^+-solute (e.g., glucose) carrier protein. The carrier has binding sites for both glucose and Na^+, and it will not traverse the membrane unless both Na^+ and glucose are attached. Glucose and Na^+ are moved into the apical portion of the enterocyte by facilitated diffusion down Na^+ concentration (140 $\rightarrow$ 15 mM) and electrical (0 $\rightarrow$ –40 mv) gradients created by the energy-dependent Na^+-K^+ pump in the basolateral membrane. This mechanism can transport glucose against its concentration gradient when necessary, that is, when intraluminal concentrations of glucose are low compared with intracellular levels. The glucose then leaves the basolateral portion of the cell and moves down its concentration gradient by facilitated diffusion. Thus, the overall movement of glucose from the intestinal lumen to the circulation is an active process deriving its energy from the Na^+-K^+ pump. A similar electrolyte-coupled transport mechanism is also important for the active absorption of other water-soluble nutrients in the small intestine (e.g., amino acids) and colon (short chain fatty acids).

Water Absorption

The absorption of water occupies a special position in gastrointestinal physiology because up to 10 liters of water are normally transported from the lumen to the blood every 24 hours. Water absorption is accomplished by osmotic forces generated by transepithelial movement of solutes from lumen-to-blood (absorption). The active transport of ions (e.g., Na^+) and organic solutes (e.g., glucose) by GI epithelium leads to the creation of an osmotic gradient between the gut lumen and intercellular spaces (Figure 1-13). The accumulation of solutes and consequent increase in osmolality within the intercellular spaces draws water across the intercellular junctions and through water channels (aquaporins) on the apical and basolateral membranes of the epithelium. The flow (and transient accumulation) of water in the intercellular compartment

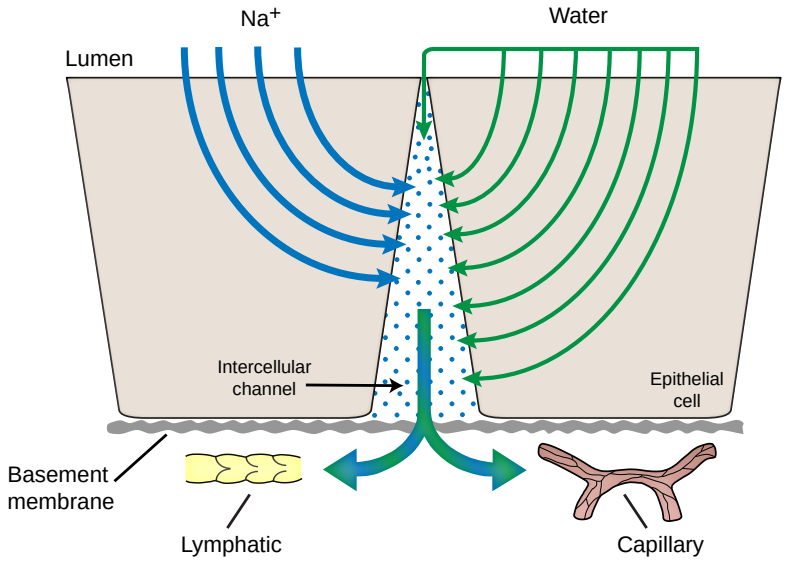

FIGURE 1-13: The standing osmotic gradient mechanism of trans-epithelial water movement. The active transport of ions (e.g., Na^+) by GI epithelium creates an osmotic gradient between the gut lumen and intercellular spaces. The increased osmolality within the intercellular spaces draws water across the intercellular junctions and through water channels (aquaporins) on the apical and basolateral membranes of the epithelium. The accumulation of water in the intercellular compartment leads to a rise in hydrostatic pressure, which drives the absorbed fluid into blood and lymphatic vessels that normally lie in close proximity to the epithelial layer.

leads to a rise in hydrostatic pressure, which in turn drives the fluid into blood and lymphatic vessels within the lamina propria that normally lie in close proximity to the epithelial layer. The osmotic pressure differences required to drive water absorption are smaller than 3 to 5 mOsm/l, which allows for water absorption by both transcellular (through cells) and paracellular (between cells) routes. It is estimated that over 50% of fluid absorption occurs through the intercellular junctions. When large volumes of water are moved through the paracellular pathway by the osmotic gradients developed during solute absorption, the phenomenon of solvent drag (convection) is observed, that is, solutes are transported due to bulk fluid motion. This passive process can mediate the movement of solutes against their electrical and chemical gradients.

Secretion

In addition to the fluid delivered to the intestines by gastric, pancreatic, and biliary secretions to facilitate digestion and absorption of nutrients, the intestines also secrete water and mucus. Intes-

tinal electrolyte-driven water secretion is derived from crypt epithelial cells, whereas mucus secretion emanates from goblet cells. Rather than subserving digestive/absorptive functions, the primary objective of these secretions is to protect the epithelium from inadvertently ingested luminal toxins. The presence of noxious material in the intestines stimulates the secretions of both water and mucus to remove the offending substances from the surface of the mucosal epithelium.

Water and Electrolyte Secretion

Secretion of electrolytes and water by the GI tract and associated glands involves mechanisms comparable to those described earlier for absorption, the major difference being the direction of solute transport, that is, lumen-to-blood movement with absorption and blood-to-lumen movement with secretion. As with absorption, an osmotic gradient is established by electrolyte secretion; therefore, water movement also occurs in the direction of blood to lumen. Parietal cells in the stomach secrete H^+ into the lumen to generate acid (HCl) for efficient protein digestion. On the other hand, pancreatic duct cells secrete HCO_3^- in the lumen to neutralize any acid entering the duodenum from the stomach. Although a major function of the intestines is to absorb the fluid load from the stomach, pancreas, and liver, the intestine also secretes electrolytes and water. Although electrolyte/water absorption normally occurs on the most luminal aspect of the epithelium (e.g., villus tips), the epithelial cells of the crypt region are the source of electrolyte/water secretion. The osmotic gradient generated by crypt cells for blood-to-lumen fluid movement is established primarily by Cl^- transport. An important physiologic benefit of water secretion from the crypts to the lumen is to ensure the fluidity of the luminal contents at the villus tips for optimal hydrolysis and absorption of ingested nutrients. In addition, the presence of noxious material in the lumen elicits an intrinsic neural reflex that increases crypt cell fluid secretion, presumably to wash away the toxins. Noxious stimuli are detected by enterochromaffin cells, which release serotonin into the interstitium. Serotonin, in turn, activates intramural afferent sensory fibers, which pass through the submucosal plexus and activate efferent secretory nerves, which release VIP at the base of the crypt cells to induce secretion.

An example for Cl^- secretion by the intestinal crypt cells is depicted in Figure 1-14. The major pathway for Cl^- secretion is the cystic fibrosis conductance regulator (CFTR) channel located at the apical membrane of intestinal crypt cells. Cl^- is taken up into the cell by a specific co-transporter in the basolateral membrane that allows for the uptake of Cl^-, K^+, and Na^+. Because this co-transporter moves 2 Cl^- (along with a Na^+ and K^+) into the cell, it provides adequate amounts of Cl^- for the secretory process. As noted above for solute-coupled Na^+ absorption (Figure 1-10), the energy required for this Na^+-K^+-2Cl^- co-transporter is derived

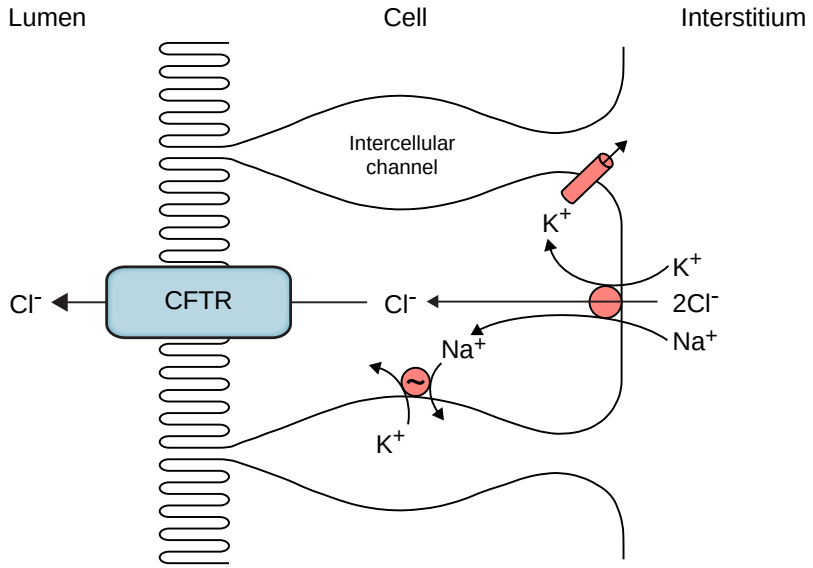

FIGURE 1-14: Mechanism of chloride secretion from the intestinal crypt cells. Cl– enters the cell via a specific co-transporter in the basolateral membrane that allows for the uptake of Cl^-, K^+, and Na+. This Na^+-K^+-$2Cl^-$ co-transporter moves 2 Cl– (along with a Na+ and K+) into the cell using energy derived from the Na+ gradient created by the Na^+-K^+ pump in the basolateral membrane. The accumulating intracellular Cl^- then moves out of the cell via the CFTR (cystic fibrosis transmembrane conductance regulator) channel.

from the Na^+ gradient created by the Na^+-K^+ pump. The accumulating intracellular Cl^- then moves out of the cell via the CFTR channel. Of note, the CFTR channel is an anion channel that can transport either Cl^- or HCO_3^-. In addition to its role in intestinal crypt cells, the CFTR channel plays an important role in electrolyte and water secretion at other sites within the gastrointestinal tract (e.g., stomach, pancreas) as well as in extra-gastrointestinal organs (e.g., lung). A dysfunctional CFTR channel is the basis for the genetic disorder, cystic fibrosis, which leads to multiorgan dysfunction that is associated with a lack of water secretion.

Mucin Secretion

Mucus is secreted by specialized epithelial cells, the gastric mucous cells and intestinal goblet cells. The major constituents of mucus that are responsible for its viscosity are the mucins; heavily glycosylated proteins. The mucin glycoproteins tend to repel each other due to the negative charges of the carbohydrate moieties. The mucin glycoproteins are stored in a compact state within gran-

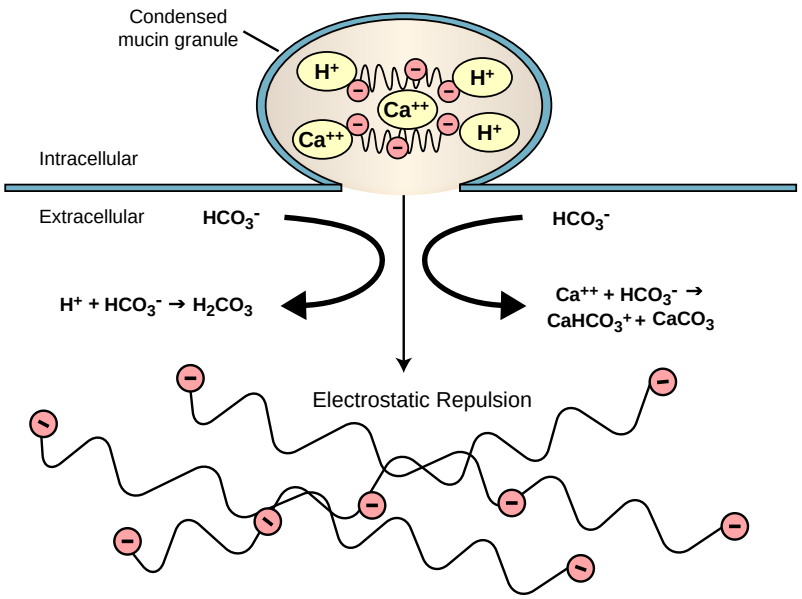

FIGURE 1-15: Schematic model of the role of HCO_3- in the formation of the mucus layer of the gastrointestinal tract. The mucin stored in goblet cells is maintained in compact form by Ca^{++} and H^+ ions that shield the negative charges. When mucin is released into the lumen, the negative charges repel each other and the mucin molecule expands; a process dependent on HCO_3- co-secretion via the CFTR channel. (Modified from *Am J Physiol Cell Physiol* 2010; 299: C1222–1233).

ules (secretory vesicles); the condensed packaging of mucins is a result of intracellular acidity and excess Ca^{++} that neutralizes the negative charges (Figure 1-15). When the granules release the mucins into the lumen, they expand dramatically in volume, spread out and organize into a sheet covering the epithelium. This process is facilitated by the co-secretion of HCO_3^- to neutralize the acid and bind the Ca^{++}, allowing the mucins to expand by electrostatic repulsion. The osmotically driven water secretion that accompanies HCO_3^- transport is quickly imbibed by the expanding mucin network. A critical anion channel integral to secretion of HCO_3^- is CFTR. Genetic deletion of CFTR results in mucoviscidosis (thick mucus) within the intestine.

The mucus layer can be subdivided into two sub-layers: an outer loose layer that can be easily removed by the passage of luminal contents and an inner layer that remains firmly adherent to the epithelium. The outer loose layer is believed to be derived from the deeper adherent layer by loosening of the network via surface digestion by luminal or bacterial enzymes. The mucus layers are not static entities, but dynamic. Removal of the outer loose layer, by motility

or the shear stress resulting from the movement of chyme, leads in its replenishment by additional secretion of mucus. The mucus layers are thick in the stomach and colon, providing a lubricating cushion that prevents damage to the gastric and colonic epithelium during the mixing and propulsion of coarse lumen contents. As mentioned above, the mucus layers in the small intestine tend to be very thin or absent, thereby allowing for absorption of nutrients from the fluid-rich chyme.

CIRCULATION OF THE DIGESTIVE SYSTEM

The digestive organs receive the largest fraction of cardiac output, that is, 25% to 30%. This high rate of perfusion is presumably required to meet the metabolic needs of this large mass of tissue. Following a meal, blood flow to all digestive organs increases to meet the enhanced demand for oxygen imposed by motility, absorption, and secretion. Inasmuch as the processes of absorption and secretion involve the transport of large volumes of fluid and solutes between the blood and gut lumen, the circulation also plays an important role in these processes.

The organization of the blood supply to the gastrointestinal tract can be characterized in terms of parallel and series coupled circuits. The three major arteries supplying the digestive organs are the celiac, superior mesenteric, and inferior mesenteric arteries (Figure 1-16). These vessels compose the parallel vascular circuit. The venous drainage from the stomach, pancreas, and intestines empties into the portal vein which, in turn, perfuses the liver and constitutes the series component of this circuit. The parallel arrangement of the splanchnic circulation allows for independent regulation of blood flow to individual organs in the GI tract, whereas the series arrangement of the portal venous system ensures that the liver is first exposed to all absorbed substances.

There are several characteristic features of the microcirculation of digestive organs that optimize the ability of these tissues to move large amounts of fluid and electrolytes between the blood and transporting epithelia. In comparison to other tissues (e.g., skeletal muscle), the digestive organs have a high capillary density and consequently a large capillary surface area for secretion or absorption. The capillaries in the digestive organs are generally of the fenestrated type. These fenestrations provide an enormous pore area for water and solute exchange. Furthermore, the fenestrations usually face the basal aspect of the transporting cell, thereby minimizing the distance fluid must travel between the blood and epithelia. Capillaries of digestive organs are highly permeable to small solutes, yet they are relatively impermeable to macromol-

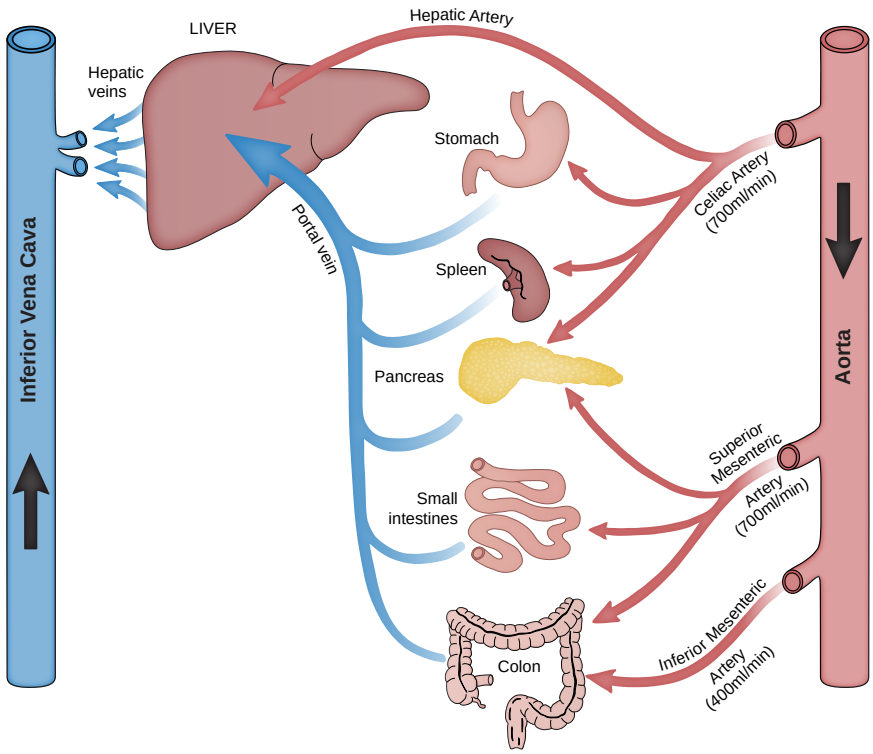

FIGURE 1-16: The splanchnic circulation. The celiac, superior mesenteric, and inferior mesenteric arteries supply blood to the organs that comprise the digestive system. The venous drainage from the spleen, stomach, pancreas, and intestines empties into the portal vein which, in turn, perfuses the liver, along with the hepatic artery (a branch of the celiac artery) (modified from *Anesthesiology* 2 2004, Vol. 100, 434–439, with permission of Wolters Kluwer Health).

ecules. This means that molecules the size of glucose readily gain access to the blood stream, whereas plasma proteins are highly restricted by the capillary wall.

Another feature of the GI microcirculation is its ability to adjust both blood flow and capillary surface area (density) to meet the oxygen requirements of digestive organs. The rate of oxygen uptake (or consumption) by the GI tract is a function of both the rate of delivery of O_2 via the blood and the capillary surface area available for O_2 diffusion. Each GI organ can regulate both blood flow and capillary density to meet its specific moment-to-moment O_2 requirements. An example of this intrinsic regulatory mechanism is illustrated in Figure 1-17, where changes in capillary density are depicted as a function of blood flow. At a normal blood

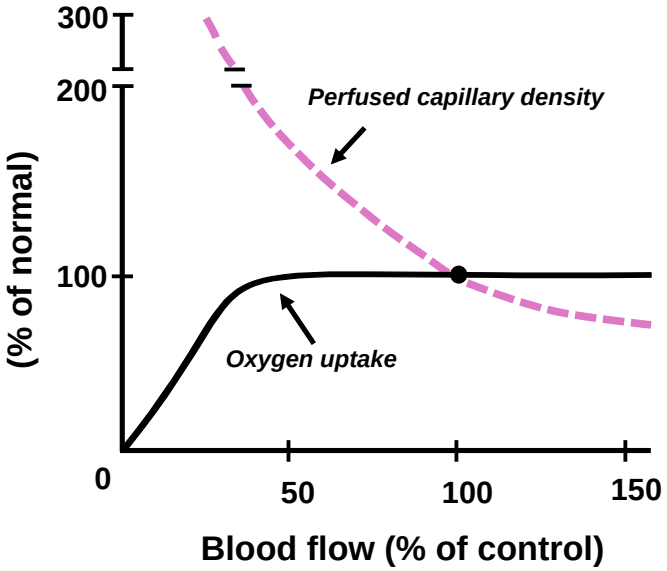

FIGURE 1-17: Gastrointestinal oxygen uptake is maintained during moderate reductions in blood flow, because the recruitment (opening) of more capillaries facilitates O_2 extraction by the tissue (increase in arteriovenous O_2 difference) when blood flow is reduced. Oxygen uptake is calculated as the product of blood flow and arteriovenous O_2 difference (modified from *Gastrointestinal Mucosal Defense System*: https://doi.org/10.4199/C00119ED1V01Y201409ISP058).

flow, approximately 25% of the capillaries are open to perfusion. If blood flow is moderately decreased, oxygen consumption remains stable because the regulatory mechanisms increase capillary density. The increase in perfused capillary density yields an increase in capillary surface area and a consequent reduction in the diffusion distance for O_2 exchange between the capillary and parenchymal cell, thereby enhancing the ability of the tissue to extract oxygen. However, with more drastic reductions in blood flow (>50%), the ability of the tissue to maintain oxygen uptake is compromised because the regulatory increase in capillary density (and O_2 extraction) is insufficient to compensate for the decrease in O_2 delivery.

Both capillary blood flow and the number of perfused capillaries in the gut increase following ingestion of a meal. These vascular responses ensure that there is an enhanced delivery of oxygen to the more metabolically active cells of the gastrointestinal tract and associated accessory organs. Furthermore, such microvascular adjustments serve to supply the water that is secreted by transporting epithelial cells of the salivary gland, pancreas, and stomach. Without

these postprandial vascular changes, the critical motor, secretory and absorptive roles of the gastrointestinal system cannot be sustained with normal digestive loads.

The lymphatic system also plays an important role in the transport functions of digestive organs. Lymphatic vessels are particularly prominent in the small bowel. Although blood flow is about 1000 times greater than lymph flow in digestive organs, approximately 1 to 2 l of lymph derived from the GI tract enters the thoracic duct each day in man. Lymph is the major route for the transport of absorbed fat into the circulation. Lymphatics also contribute to the removal of absorbed water from the small and large bowels.

PATHOPHYSIOLOGY AND CLINICAL CORRELATIONS

Figure 1-18 illustrates the relationships among GI oxygen consumption (uptake), epithelial solute transport (absorptive or secretory), and tissue injury, relative to blood flow. Moderate (<50%) reductions in blood flow do not compromise tissue oxygen uptake and do not affect absorptive or secretory activity in the GI tract. However, more severe reductions in blood flow that lead to a reduction in tissue oxygen uptake can have an adverse effect on GI function. For example, gastric acid secretion or intestinal glucose absorption are compromised once blood flow is reduced to levels that limit oxygen uptake, that is, solute transport become limited by blood flow and oxygen delivery. A similar relationship is noted with gastrointestinal motor activity; motility becomes dependent on blood flow only when blood flow is reduced to levels that compromise oxygen uptake. Tissue injury does not become apparent until oxygen consumption is reduced by ≥50%.

Acute mesenteric ischemia is a syndrome resulting from inadequate blood flow in the mesenteric vessels. From a pathophysiologic standpoint, the bowel is resilient to reductions in blood flow. Ischemia results when blood flow is not adequate to provide critical levels of oxygen. Collaterals will develop shortly after vessel obstruction develops distal to the obstructive site. With prolonged ischemia, vasoconstriction develops (due to angiotensin II, vasopressin, and prostaglandins) that eventually leads to irreversible ischemia. With the restoration of blood flow (reperfusion), further tissue injury can result, due in part from the generation of reactive oxygen species and the recruitment and activation of inflammatory cells. Mesenteric ischemia presents with abdominal pain that typically results from embolic occlusion or thrombosis of the superior mesenteric artery. The pain may be focal or present diffusely. Infections and tissue necrosis may develop if emergent therapy, using interventional radiologic or surgical approaches, is not initiated to restore blood flow to the affected organ. In *chronic mesenteric ischemia*, postprandial

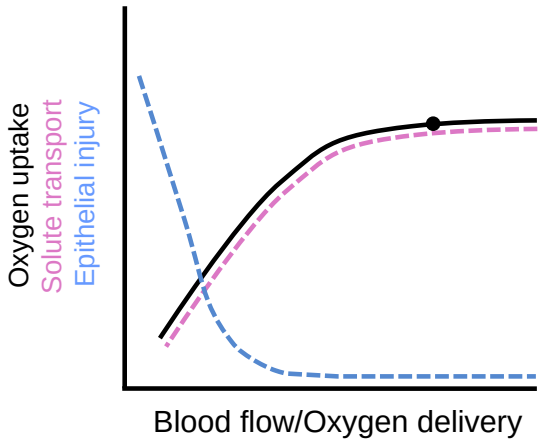

FIGURE 1-18: Reductions in GI blood flow yield parallel reductions in epithelial solute transport and tissue oxygen uptake. However, epithelial injury is not manifested until blood flow is reduced to levels yielding >50% decline in oxygen uptake (modified from *Gastrointestinal Mucosal Defense System*: https://doi.org/10.4199/C00119ED1V01Y201409ISP058).

abdominal pain or "intestinal angina" may develop shortly (less than half an hour) after a meal, resolving in 1 to 3 hours. A more extensive collateral circulation develops with atherosclerotic narrowing of the major vessels, which occurs predominantly in the elderly. Treatment can involve surgical revascularization or endovascular recanalization with mesenteric angioplasty.

Ischemic colitis is the most common form of ischemic injury in the GI tract. This condition is often seen in the elderly with underlying cardiovascular disease. Low blood flow in the inferior mesenteric artery or colonic branches of the superior mesenteric artery can lead to edema, submucosal hemorrhage and an inflammatory response in the affected bowel segment. The predominant symptom is left lower quadrant abdominal pain associated with abdominal distension and need to defecate; diarrhea and hematochezia (passage of fresh blood through the anus) may also develop. In a patient with right-sided colitis, the pain in focused in the lower abdomen and may not be associated with bloody diarrhea. Diagnosis is made based on history, physical examination findings and endoscopic evaluation. The colonoscope is used to identify the location of the ischemic segment, and this procedure is completed with minimal air or carbon dioxide insufflation. Biopsies may be taken for confirmation histologically, unless the colitis is severe, which would increase risk for bowel perforation. Treatment is mostly supportive with intravenous fluids and broad-spectrum antibiotics due to the potential for spontaneous recovery within 1 to 3 weeks. Occasionally, ischemic strictures, resulting in obstruction, or gangrene (peritonitis) may develop that requires surgical intervention.

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