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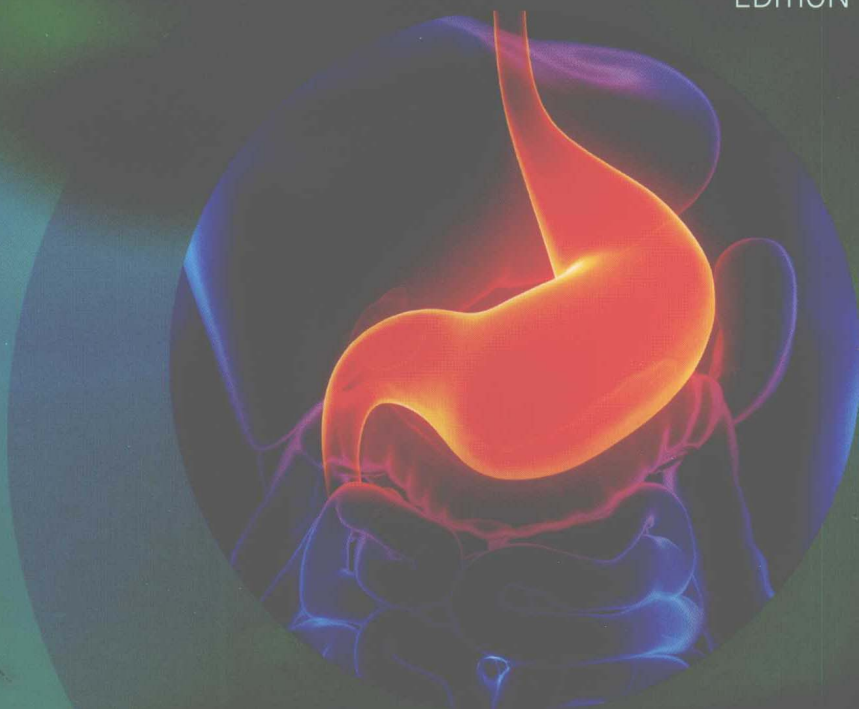
Leonard R. Johnson

GASTROINTESTINAL PHYSIOLOGY

8th EDITION



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Gastrointestinal Physiology

Eighth Edition

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PREFACE

The first edition of *Gastrointestinal Physiology* appeared in 1977. It developed as a result of the authors' teaching experiences and the need for a book on gastrointestinal physiology written and designed for medical students and beginning graduate students. This eighth edition is directed to the same audience. As with any new edition, I believe that it is significantly better than the previous one. All chapters contain considerable amounts of new material and have been brought up-to-date with current information, without introducing undue amounts of controversy to confuse students. New figures have been added, others updated, and some chapters significantly rewritten.

Major changes in this edition are the addition of a list of "Objectives" at the beginning of chapters and "Clinical Applications" boxes within chapters. Hopefully the learning objectives will provide a guide to the important concepts and be an aid to understanding them. The material presented as clinical applications is meant to emphasize the significance of some of the basic science, provide some perspective, and increase student interest.

I am grateful to my own students for pointing out ways to improve the book. Numerous colleagues in other medical schools and professional institutions have added their suggestions and criticisms as well. I am thankful for their interest and help, and I hope that anyone having criticisms of this edition or suggestions for improving future editions will transmit them to me.

This is the first edition appearing under sole authorship. In all previous editions, the motility chapters were written by Dr. Norman W. Weisbrodt, who has since retired. I am grateful to him for allowing me to use his material as I saw fit.

I would like to thank H.J. Ehrlein and Michael Schemann for generously allowing us to link the videos referenced in Chapters 4 and 5, which appear on the website of the Technische Universität München (http://www.wzw.tum.de/humanbiology/data/motility/34/?alt=english). The videofluoroscopy on gastrointestinal motility of dogs, pigs, and sheep was performed during the scientific studies of H.J. Ehrlein and his colleagues over a period of 25 years. This video project was supported by an educational grant from Janssen Research Foundation.

Finally, I thank Ms. Marybeth Thiel of Elsevier for suggestions and for helping with the communications and organizational work that are a necessary part of such a project.

LEONARD R. JOHNSON

CONTENTS

1 REGULATION: PEPTIDES OF THE GASTROINTESTINAL TRACT

OBJECTIVES

- Describe the four major functions of the gastrointestinal (GI) tract.
- Understand the differences between and significance of endocrine, paracrine, and neurocrine agents.
- Identify the major GI hormones, their functions, sites of release, and stimuli for release.
- Identify the important neurocrines and their functions in the GI tract.
- Identify the important paracrines and their functions in the GI tract.
- Understand the causes and resulting physiology of gastrinoma (Zollinger-Ellison syndrome) and pancreatic cholera (Werner Morrison syndrome).

The functions of the gastrointestinal (GI) tract are regulated by peptides, derivatives of amino acids, and a variety of mediators released from nerves. All GI hormones are peptides, but it is important to realize that not all peptides found in digestive tract mucosa are hormones. The GI tract peptides can be divided into endocrines, paracrines, and neurocrines, depending on the method by which the peptide is delivered to its target site.

Endocrines, or **hormones,** are released into the general circulation and reach all tissues (unless these substances are excluded from the brain by the blood-brain barrier). Specificity is a property of the target tissue itself. Specific receptors, which recognize and bind the hormone, are present on its target tissues and absent from others. There are five established GI hormones; in addition, some GI peptides are released from endocrine cells into the blood but have no known physiologic function. Conversely, several peptides have been isolated from mucosal tissue and have potent GI effects, but no mechanism for their physiologic release has been found. Members of these latter two groups are classified as candidate hormones.

Paracrines are released from endocrine cells and diffuse through the extracellular space to their target tissues. Their effects are limited by the short distances necessary for diffusion. Nevertheless, these agents can affect large areas of the digestive tract by virtue of the scattered and abundant distributions of the cells containing them. A paracrine agent can also act on endocrine cells. Thus a paracrine may release or inhibit the release of an endocrine substance, thereby ultimately regulating a process remote from its origin. Histamine, a derivative of the amino acid histidine, is an important regulatory agent that acts as a paracrine.

Some GI peptides are located in nerves and may act as **neurocrines** or neurotransmitters. A neurocrine is released near its target tissue and needs only to diffuse across a short synaptic gap. Neurocrines conceivably may stimulate or inhibit the release of endocrines or paracrines. **Acetylcholine** (ACh), although not a peptide, is an important neuroregulator in the GI tract. One of its actions is to stimulate acid secretion from the gastric parietal cells.

GENERAL CHARACTERISTICS

The GI tract is the largest endocrine organ in the body, and its hormones were the first to be discovered. The word *hormone* was coined by W. B. Hardy and used by Starling in 1905 to describe secretin and gastrin and to

convey the concept of bloodborne chemical messengers. The GI hormones are released from the mucosa of the stomach and small intestine by nervous activity, distention, and chemical stimulation coincident with the intake of food. Released into the portal circulation, the GI hormones pass through the liver to the heart and back to the digestive system to regulate its movements, secretions, and growth. These hormones also regulate the growth of the mucosa of the stomach and small and large intestines, as well as the growth of the exocrine pancreas.

The GI peptides have many different types of actions. Their effects on water, electrolyte, and enzyme secretion are well known, but they also influence motility, growth, and release of other hormones, as well as intestinal absorption. Many of these actions overlap; two or more GI peptides may affect the same process in the same direction, or they may inhibit each other. Many of the demonstrated actions of these peptides are pharmacologic and do not occur under normal circumstances. This chapter is concerned primarily with the physiologic effects of the GI peptides.

The actions of the GI peptides also may vary in both degree and direction among species. The actions discussed in the remainder of this chapter are those occurring in humans.

DISCOVERY

Four steps are required to establish the existence of a GI hormone. First, a physiologic event such as a meal must be demonstrated to provide the stimulus to one part of the digestive tract that subsequently alters the activity in another part. Second, the effect must persist after all nervous connections between the two parts of the GI tract have been severed. Third, from the site of application of the stimulus a substance must be isolated that, when injected into the blood, mimics the effect of the stimulus. Fourth, the substance must be identified chemically, and its structure must be confirmed by synthesis.

Five GI peptides have achieved full status as hormones. They are secretin, gastrin, cholecystokinin (CCK), gastric inhibitory peptide (GIP), and motilin. There is also an extensive list of "candidate" hormones whose significance has not been established. This list includes several chemically defined peptides that have significant actions in physiology or pathology but whose hormonal status has not been proved. These are pancreatic polypeptide, neurotensin, and substance P. In addition, two known hormones, glucagon and somatostatin, have been identified in GI tract mucosa; their possible function as GI hormones is currently being investigated. Some of these peptides function physiologically as paracrines or neurocrines. Another GI peptide, **Ghrelin,** is released from the body of the stomach and functions as a hormone to regulate food intake. This topic is covered in Chapter 13.

Secretin, the first hormone, was discovered in 1902 by Bayliss and Starling and was described as a substance, released from the duodenal mucosa by hydrochloric acid, that stimulated pancreatic bicarbonate and fluid secretion. Jorpes and Mutt isolated it and identified its amino acid sequence in 1966. It was synthesized by Bodanszky and coworkers later the same year.

Edkins discovered gastrin in 1905, stating to the Royal Society that "in the process of the absorption of digested food in the stomach a substance may be separated from the cells of the mucous membrane which, passing into the blood or lymph, later stimulates the secretory cells of the stomach to functional activity." For 43 years investigators were preoccupied by the controversy over the existence of gastrin. The debate intensified when Popielski demonstrated that histamine, a ubiquitous substance present in large quantities throughout the body (including the gastric mucosa), was a powerful gastric secretagogue. In 1938 Komarov demonstrated that gastrin was a polypeptide and was different from histamine. By 1964 Gregory and his colleagues had extracted and isolated hog gastrin; Kenner and his group synthesized it the same year. After 60 years all of the criteria for establishing the existence of a GI hormone had been satisfied.

In 1928 Ivy and Oldberg described a humoral mechanism for the stimulation of gallbladder contraction initiated by the presence of fat in the intestine. The hormone was named cholecystokinin after its primary action. The only controversy involving CCK was a mild one over nomenclature. In 1943 Harper and Raper described a hormone released from the small intestine that stimulated pancreatic enzyme secretion and accordingly named it *pancreozymin.* As Jorpes and Mutt carried out the purification of these two substances in 1968, it became obvious that both properties

resided in the same peptide. For the sake of convenience and because it was the first action described, this hormone is called CCK.

In 1969 Brown and his coworkers described the purification of a powerful enterogastrone from intestinal mucosa. Enterogastrone literally means a substance from the intestine *(entero-)* that inhibits *(-one)* the stomach *(gastr-)*. By 1971 this peptide had been purified, isolated, sequenced, and named gastric inhibitory peptide for its ability to inhibit gastric secretion. Released from the intestinal mucosa by fat and glucose, GIP also stimulates insulin release. Following proof that the release of insulin was a physiologic action of the peptide, GIP became the fourth GI hormone. The insulinotropic effect of GIP requires elevated amounts of serum glucose. For this reason, and because it is doubtful whether the inhibitory effects of the peptide on the stomach are physiologic, it has been suggested that its name be changed to glucose-dependent insulinotropic peptide. In either case it is still referred to as GIP.

Brown and his coworkers also described the purification of motilin in the early 1970s. Motilin is a linear 22–amino acid peptide purified from the upper small intestine. During fasting it is released cyclically and stimulates upper GI motility. Its release is under neural control and accounts for the interdigestive migrating myoelectric complex.

CHEMISTRY

The GI hormones and some related peptides can be divided into two structurally homologous families. The first consists of gastrin (Fig. 1-1) and CCK (Fig. 1-2). The five carboxyl-terminal (C-terminal) amino acids are identical in these two hormones. All the biologic activity of gastrin can be reproduced by the four C-terminal amino acids. This tetrapeptide, then, is the minimum fragment of gastrin needed for strong activity and is about one sixth as active as the whole 17–amino acid molecule. The sixth amino acid from the C-terminus of gastrin is tyrosine, which may or may not be sulfated. When sulfated, the hormone is called gastrin II. Both forms occur with equal frequency in nature. The amino-terminus (N-terminus) of gastrin is pyroglutamyl, and the C-terminus is phenylalamide (see Fig. 1-1). The NH_2 group following Phe does not signify that this is the N-terminus; rather, it indicates that this C-terminal amino acid is amidated. These alterations in structure protect the molecules from aminopeptidases and carboxypeptidases and allow most of them to pass through the liver without being inactivated.

Gastrin is first synthesized as a large, biologically inactive precursor called progastrin. A glycine-extended (**G-Gly**) form of gastrin is then formed by endoproteolytic processing within the G cells. G-Gly is the substrate for an amidation reaction that results in the formation of the mature, amidated gastrin. The C-terminal amide moiety is required for full biologic activity mediated by gastrin/CCK-2 receptors. Receptors for CCK and gastrin were originally called the CCK-A and CCK-B receptors, respectively; the

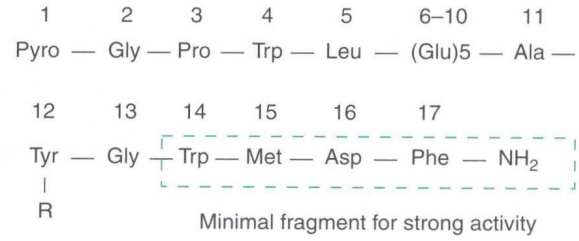

FIGURE 1-1 ■ Structure of human little gastrin (G 17).

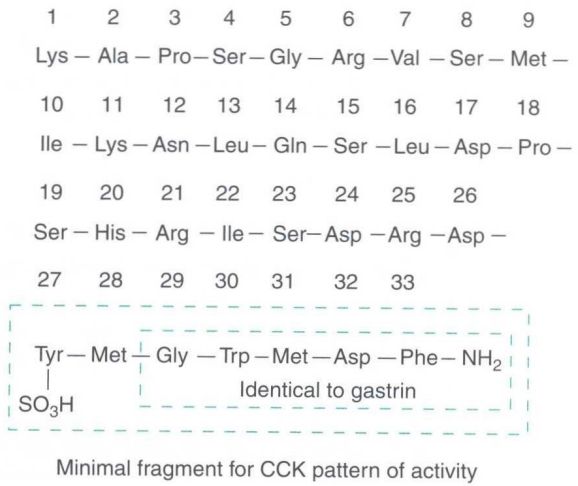

FIGURE 1-2 ■ Structure of porcine cholecystokinin (CCK).

nomenclature has been changed to CCK-1 and CCK-2. G-Gly does not stimulate the gastrin/CCK-2 receptor but instead activates its own receptor, thus leading to the activation of Jun kinase and trophic effects.

CCK, which has 33 amino acids, contains a sulfated tyrosyl residue in position 7 from the C-terminus (see Fig. 1-2). CCK can activate gastrin receptors (e.g., those for acid secretion, also called CCK-2 receptors); gastrin can activate CCK receptors (e.g., those for gallbladder contraction, also called CCK-1 receptors). Each hormone, however, is more potent at its own receptor than at those of its homologue. CCK is always sulfated in nature, and desulfation produces a peptide with the gastrin pattern of activity. The minimally active fragment for the CCK pattern of activity is therefore the C-terminal heptapeptide.

In summary, peptides belonging to the gastrin/CCK family having a tyrosyl residue in position 6 from the C-terminus or an unsulfated one in position 7 possess the gastrin pattern of activity and act on CCK-2 receptors—strong stimulation of gastric acid secretion and weak contraction of the gallbladder. Peptides with a sulfated tyrosyl residue in position 7 act on CCK-1 receptors, have cholecystokinetic potency, and are weak stimulators of gastric acid secretion. Obviously the tetrapeptide itself and all fragments less than seven amino acids long possess gastrin-like activity.

The second group of peptides is homologous to secretin and includes **vasoactive intestinal peptide** (VIP), GIP, and **glucagon,** in addition to secretin (Fig. 1-3). Secretin has 27 amino acids, all of which are required for substantial activity. Pancreatic glucagon has 29 amino acids, 14 of which are identical to those of secretin. Glucagon-like immunoreactivity has been isolated from the small intestine, but the physiologic significance of this **enteroglucagon** has not been established. Glucagon has no active fragment, and, like secretin, the whole molecule is required before any activity is observed. Evidence indicates that secretin exists as a helix; thus the entire amino acid sequence may be necessary to form a tertiary structure with biologic activity.

GIP and VIP each have nine amino acids that are identical to those of secretin. Each has many of the same actions as those of secretin and glucagon. This group of peptides is discussed in greater detail later in the chapter.

Most peptide hormones are heterogeneous and occur in two or more molecular forms. Gastrin, secretin, and CCK all have been shown to exist in more than one form. Gastrin was originally isolated from hog antral mucosa as a heptadecapeptide (see Fig. 1-1), which is now referred to as little gastrin (G 17). It accounts for 90% of antral gastrin. Yalow and Berson demonstrated heterogeneity by showing that the major component of gastrin immunoactivity in the serum was a larger molecule that they called big gastrin. On isolation, big gastrin was found to contain 34 amino acids; hence it is called G 34. Trypsin splits G 34 to yield G 17 plus a heptadecapeptide different from G 17. Therefore, G 34 is not simply a dimer of G 17.

	*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Secretin	(27)	His–	Ser–	Asp–	Gly–	Thr–	Phe–	Thr–	Ser–	Glu–	Leu–	Ser–	Arg–	Leu–	Arg–	Asp–
VIP	(28)				Ala–	Val–			Asp–	Asn–	Tyr–	Thr–				Lys–
GIP	(42)	Tyr–	Ala–	Glu–				Ile–		Asp–	Tyr–		Ile–	Ala–	Met	
Glucagon	(29)			Gln–						Asp–	Tyr–		Lys–	Tyr–	Leu	

	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Secretin	Ser–	Ala–	Arg–	Leu–	Gln–	Arg–	Leu–	Leu–	Gln–	Gly–	Leu–	Val–	NH_2–	
VIP	Gln–	Met–	Ala–	Val–	Lys–	Lys–	Tyr–		Asn–	Ser–	Ile–	Leu–	Asn–	NH_2–
GIP	Lys–	Ile		Gln–		Asp–	Phe–	Val–	Asn–	Trp–		Leu–	Ala–	Gln–14 more
Glucagon		Arg–		Ala–		Asp–	Phe–	Val–		Trp–		Met–	Asp–	Thr

* Total amino acid residues
Blank spaces indicate residues identical to those in secretin.

FIGURE 1-3 ■ Structures of the secretin family of peptides. GIP, gastric inhibitory peptide; VIP, vasoactive intestinal peptide.

An additional gastrin molecule (G 14) has been isolated from tissue and contains the C-terminal tetradecapeptide of gastrin. Current evidence indicates that most G 17 is produced from pro G 17 and most G 34 is derived from pro G 34. Thus G 34 is not a necessary intermediate in the production of G 17.

During the interdigestive (basal) state, most human serum gastrin is G 34. Unlike those of other species, the duodenal mucosa of humans contains significant amounts of gastrin. This is primarily G 34 and is released in small amounts during the basal state. After a meal, a large quantity of antral gastrin, primarily G 17, is released and provides most of the stimulus for gastric acid secretion. Smaller amounts of G 34 are released from both the antral and the duodenal mucosa. G 17 and G 34 are equipotent, although the half-life of G 34 is 38 minutes and that of G 17 is approximately 7 minutes. The plasma concentration of gastrin in fasting humans is 10 to 30 pmol/L, and it doubles or triples during the response to a normal mixed meal.

DISTRIBUTION AND RELEASE

The GI hormones are located in endocrine cells scattered throughout the GI mucosa from the stomach through the colon. The cells containing individual hormones are not clumped together but are dispersed among the epithelial cells. The nature of this distribution makes it virtually impossible to remove the source of one of the GI hormones surgically and examine the effect of its absence without compromising the digestive function of the animal.

The endocrine cells of the gut are members of a widely distributed system termed **amine precursor uptake decarboxylation** (APUD) cells. These cells all are derived from neuroendocrine-programmed cells originating in the embryonic ectoblast.

The distributions of the individual GI hormones are shown in Figure 1-4. Gastrin is most abundant in the antral and duodenal mucosa. Most of its release under physiologic conditions is from the antrum. Secretin, CCK, GIP, and motilin are found in the duodenum and jejunum.

Ultrastructurally, GI endocrine cells have hormone-containing granules concentrated at their bases, close to the capillaries. The granules discharge, thereby releasing their hormones in response to events that are either the direct or the indirect result of neural, physical, and chemical stimuli associated with eating a meal and the presence of that meal within the digestive tract. These endocrine cells have microvilli on their apical borders that presumably contain receptors for sampling the luminal contents.

Table 1-1 lists the stimuli that are physiologically important releasers of the GI hormones. Gastrin and motilin are the only hormones shown to be released directly by neural stimulation. Protein in the form of peptides and single amino acids releases both gastrin and CCK. Fatty acids containing eight or more carbon atoms or their monoglycerides are the most potent stimuli for CCK release. Fat must be broken down into an absorbable form before release of CCK, thus providing evidence that the receptors for release are triggered during the process of absorption.

Evidence indicates that intestinal releasing factors secreted into the intestine of certain species, including humans, stimulate the release of CCK. Pancreatic enzymes inactivate these releasing factors. The ingestion and presence of a meal in the intestine result in

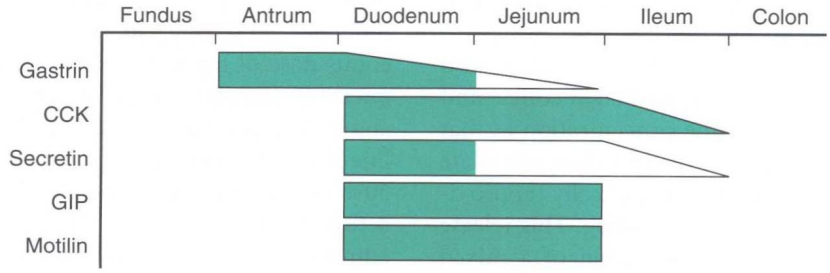

FIGURE 1-4 ■ Distribution of the gastrointestinal hormones. *Shaded areas* indicate where the most release occurs under normal conditions. CCK, cholecystokinin; GIP, gastric inhibitory peptide.

TABLE 1-1
Releasers of Gastrointestinal Hormones

	HORMONE				
Releaser	*Gastrin*	*CCK*	*Secretin*	*GIP*	*Motilin*
Protein	S	S	0	S	0
Fat	0	S	S-	S	S-
Carbohydrate	0	0	0	S	0
Acid	I	S-	S	0	S-
Distention	S	0	0	0	0
Nerve	S	0	0	0	S

CCK, cholecystokinin; GIP, gastric inhibitory peptide; I, inhibits release physiologically; S, physiologic stimulus for release; S-, of secondary importance; 0, no effect.

temporary binding of trypsin and other proteases and allow the releasing factors to remain active and stimulate CCK secretion. Thus this mechanism acts as a negative feedback control on pancreatic enzyme secretion.

Carbohydrate, the remaining major foodstuff, does not alter the release of gastrin, secretin, or CCK to a significant extent but does stimulate GIP release. GIP also is released by fat and protein. The strongest stimulus for secretin release is H^+. Secretin is released when the pH in the duodenum falls below 4.5. Secretin also is released by fatty acids. This may be a significant mechanism for secretin release because the concentration of fatty acids in the lumen is often high. CCK can also be released by acid, but except during hypersecretion of acid, the physiologic significance of this mechanism of release has not been established. The purely physical stimulus of distention activates antral receptors and causes gastrin release; for example, inflating a balloon in the antrum releases gastrin. During a meal the pressure of ingested food initiates this response. The magnitude of the response is not as great as originally believed, however, and the contribution of distention to the total amount of gastrin released in humans probably is minor. Gastrin also can be released by calcium, decaffeinated coffee, and wine. Pure alcohol in the same concentration as that of wine does not release gastrin but does stimulate acid secretion. Motilin is released cyclically (approximately every 90 minutes) during fasting. This release is prevented by atropine and ingestion of a mixed meal. Acid and fat in the duodenum, however, increase motilin release.

In addition to releasing secretin, acid exerts an important negative feedback control of gastrin release. Acidification of the antral mucosa below a pH of 3.5 inhibits gastrin release. Patients with atrophic gastritis, pernicious anemia, or other conditions characterized by the chronic decrease of acid-secreting cells and hyposecretion of acid may have extremely high serum concentrations of gastrin because of the absence of this inhibitory mechanism.

Hormones alter the release of GI peptides in several instances. Both secretin and glucagon, for example, inhibit gastrin release. CCK has been shown to stimulate glucagon release, and four GI hormones (secretin, gastrin, CCK, and GIP) increase insulin secretion. Elevated serum calcium stimulates both gastrin and CCK release. It is doubtful whether any of these mechanisms, with the exception of release of insulin by GIP, play a role in normal GI physiology. Some mechanisms, however, may become important when circulating levels of hormones or calcium are altered by disease.

ACTIONS AND INTERACTIONS

The effects of pure GI hormones have been tested on almost every secretory, motor, and absorptive function of the GI tract. Each peptide has some action on almost every target tested. Even though large doses of hormone sometimes are necessary to produce an effect, either stimulatory or inhibitory, these tests indicate that receptors for each hormone are present on most target tissues. The myriad activities possessed by these peptides are summarized in Table 1-2.

The important physiologic actions of the GI hormones are depicted in Table 1-3. Numerous guidelines have been proposed for determining whether an action is physiologic. The action should occur in response to endogenous hormone released by normal stimuli (i.e., those present during a meal). In other words, an exogenous dose of hormone should produce the effect in question without elevating serum hormone levels above those produced by a meal. An acceptable guideline for exogenous infusion is a dose that produces 50% of the maximal response (D_{50}) of the primary action of the hormone. The hormone should be administered as a continuous intravenous infusion rather than as a single bolus because the a bolus produces transient, unphysiologically high serum levels.

TABLE 1-2
Actions of Gastrointestinal Hormones

	HORMONE				
Action	*Gastrin*	*CCK*	*Secretin*	*GIP*	*Motilin*
Acid secretion	S	S	I	I	
Gastric emptying	I	I	I	I	
Pancreatic HCO_3^- secretion	S	S	S	0	
Pancreatic HCO_3^- enzyme secretion	S	S	S	0	
Bile HCO_3^- secretion	S	S	S	0	
Gallbladder contraction	S	S	S		
Gastric motility	S	S	I	I	S
Intestinal motility	S	S	I		S
Insulin release	S	S	S	S	
Mucosal growth	S	S	I		
Pancreatic growth	S	S	S		

CCK, cholecystokinin; GIP, gastric inhibitory peptide; HCO_3^-, bicarbonate; I, inhibits; S, stimulates;
0, no effect; *blank spaces,* not yet tested.

TABLE 1-3
Important Actions of Gastrointestinal Hormones

	HORMONE				
Action	*Gastrin*	*CCK*	*Secretin*	*GIP*	*Motilin*
Acid secretion	S		I	I	
Pancreatic HCO_3^- secretion		S	S		
Pancreatic enzyme secretion		S			
Bile HCO_3^- secretion			S		
Gallbladder contraction		S			
Gastric emptying		I			
Insulin release			S		
Mucosal growth	S				
Pancreatic growth		S	S		
Gastric motility					S
Intestinal motility					S

CCK, cholecystokinin; GIP, gastric inhibitory peptide; HCO_3^-, bicarbonate; I, inhibits; S, stimulates.

The primary action of gastrin is the stimulation of gastric acid secretion. It does this by causing the release of histamine (a potent acid secretagogue) from the **enterochromaffin-like** (ECL) cells of the stomach and by direct action on the parietal cells. Gastrin is the most important regulator of gastric acid secretion. There is considerable debate on the role of gastrin in regulating the tone of the lower esophageal sphincter, and the bulk of the evidence indicates no normal role for gastrin in regulation.

One of the most important and more recently discovered actions of GI hormones is their trophic activity. Gastrin stimulates synthesis of ribonucleic acid (RNA), protein, and deoxyribonucleic acid (DNA), as well as growth of the mucosa of the small intestine, colon, and oxyntic gland area of the stomach. If most endogenous gastrin is removed by antrectomy, these tissues atrophy. Exogenous gastrin prevents this atrophy. Patients with tumors that constantly secrete gastrin exhibit hyperplasia and hypertrophy of the acid-secreting portion of the stomach. Gastrin also stimulates the growth of ECL cells. Continued hypersecretion of gastrin results in ECL cell hyperplasia, which may develop into carcinoid tumors. The trophic effects of gastrin are restricted to GI tissues and are counteracted by secretin. The trophic action of gastrin is a direct effect that can be demonstrated in tissue culture.

As mentioned previously, G-Gly also has trophic effects. G-Gly is far less potent (by at least four orders of magnitude) than gastrin in stimulating gastric acid secretion. However, G-Gly is stored in gut tissues, is secreted with gastrin from antral G cells, and reaches concentrations in plasma equal to those of gastrin. Although antagonists of the CCK-B/gastrin receptor block the trophic effects of gastrin, they have no effect on the growth-promoting actions of G-Gly. Additional evidence suggests that the growth-related receptors for G-Gly work in concert with gastrin to regulate the functional development of the gut.

The primary effect of secretin is the stimulation of pancreatic fluid and bicarbonate secretion; one of the primary actions of CCK is the stimulation of pancreatic enzyme secretion. In addition, CCK has a physiologically important interaction in potentiating the primary effect of secretin. Thus CCK greatly increases the pancreatic bicarbonate response to low circulating levels of secretin.

Both CCK and secretin also stimulate the growth of the exocrine pancreas. CCK exerts a stronger effect than secretin, but the combination of the two hormones produces a potentiated response in rats that is truly remarkable. It is likely that the effects of these two hormones on pancreatic growth are as important as their effects on pancreatic secretion.

In addition to its effects on the pancreas, secretin stimulates biliary secretion of fluid and bicarbonate. This action is shared by CCK, but secretin is the most potent choleretic of the GI hormones. In dogs, secretin is a potent inhibitor of gastrin-stimulated acid secretion. This action is probably not physiologically important in humans. The ability of secretin to inhibit acid secretion may be important in some human diseases, however, and students should be aware of this action. Secretin has been nicknamed "nature's antacid" because almost all its actions reduce the amount of acid in the duodenum. The only known exception to this statement is secretin's pepsigogic activity. Secretin is second only to ACh in promoting pepsinogen secretion from the chief cells of the stomach. Because only small amounts of secretin are released under normal circumstances, it is doubtful whether secretin stimulates pepsin secretion physiologically.

In addition to its physiologic actions on pancreatic and biliary secretion, CCK regulates gallbladder contraction and gastric emptying. Of the GI peptides, CCK is the most potent regulator of gallbladder contraction; it is approximately 100 times more effective than the gastrin tetrapeptide in contracting the gallbladder. CCK causes significant inhibition of gastric emptying in doses equal to the D_{50} of pancreatic secretion. Gastrin also inhibits gastric emptying, but the effective dose is approximately 6 times the D_{50} for stimulation of acid secretion by gastrin. These data support the conclusions that CCK physiologically inhibits gastric emptying and gastrin does not.

CCK also functions to regulate food intake. It was the first satiety hormone to be discovered, and this action is fully covered in Chapter 13.

Several peptides, including secretin and GIP, are enterogastrones. GIP was originally discovered because of its ability to inhibit gastric acid secretion, and it may well have been the original enterogastrone described by Ivy and Farrell in 1925. Its action has not been established as physiologically significant in the innervated stomach. GIP, however, is a strong stimulator of insulin release and is responsible for the fact that an oral glucose load releases more insulin and is metabolized more rapidly than an equal amount of glucose administered intravenously.

Motilin stimulates the so-called migrating motility or myoelectric complex that moves through the stomach and small bowel every 90 minutes in the fasted GI tract. Its cyclic release into the blood is inhibited by the ingestion of a meal. This is the only known function of this peptide.

CANDIDATE HORMONES

Earlier in this chapter, certain peptides isolated from digestive tract tissue were mentioned that may, at a later date, qualify as hormones. These often are referred to as *candidate,* or *putative, hormones.* Many have been proposed, but interest is greatest for those listed in Table 1-4. Enteroglucagon belongs to the secretin family. Pancreatic polypeptide and peptide YY (tyrosine-tyrosine) belong to a separate family and are unrelated to either gastrin or secretin.

Pancreatic polypeptide was first identified as a minor impurity in insulin. It was then isolated and found to be a linear peptide with 36 amino acid residues. From a physiologic viewpoint the most important action of pancreatic polypeptide is the inhibition of both pancreatic bicarbonate and enzyme secretion because this effect has the lowest dose requirement. Most constituents of a meal release pancreatic polypeptide, and the serum levels reached are sufficient to

TABLE 1-4
Candidate Hormones

Peptide	*Released By*	*Action(s)*
Pancreatic polypeptide	Protein Fat Glucose	↓Pancreatic HCO_3^- and enzyme secretion
Peptide YY	Fat	↓Gastric secretion ↓Gastric emptying
Enteroglucagon	Hexose Fat	↓Gastric secretion ↓Gastric emptying ↑Insulin release

↓, inhibits; ↑, stimulates; HCO_3^-, bicarbonate.

inhibit pancreatic secretion. Because the peak rate of pancreatic secretion during a meal is less than the maximal rate that can be achieved with exogenous stimuli, it is possible that pancreatic polypeptide modulates this response under normal conditions. Before it can be concluded that pancreatic polypeptide is responsible for the physiologic inhibition of pancreatic secretion, it must be shown that this actually occurs and that pancreatic polypeptide is the causative agent. The fact that the peptide is located in the pancreas and cannot be removed without also removing its target organ makes this evidence difficult to obtain.

Peptide YY was discovered in porcine small intestine and was named for its N-terminal and C-terminal amino acid residues—both tyrosines. Of its 36 amino acid residues, 18 are identical to those of pancreatic polypeptide. Peptide YY is released by meals, especially by fat. It may appear in plasma in concentrations sufficient to inhibit gastric secretion and emptying and thus qualifies as an enterogastrone. Its effects do not appear to be direct in that it does not inhibit secretion in response to gastrin or histamine. It does inhibit neurally stimulated secretion, but its final status as an enterogastrone has not been determined. Peptide YY also inhibits intestinal motility, and this effect is believed by some investigators to enhance luminal nutrient digestion and absorption.

The enteroglucagons are products of the same gene processed in the pancreatic alpha cell to form glucagon. The intestinal L cell makes three forms of glucagon, one of which, glucagon-like peptide-1 (GLP-1), may have important physiologic actions. This 30–amino acid peptide is a potent insulin releaser, even in the absence of hyperglycemia, and it also inhibits gastric secretion and emptying. GLP-1 may mediate the so-called ileal brake—the inhibition of gastric and pancreatic secretion and motility that occurs when lipids and/or carbohydrates are infused into the ileum in amounts sufficient to cause malabsorption.

NEUROCRINES

All GI peptides were once believed to originate from endocrine cells and therefore to be either hormones or candidate hormones. With the advent of sophisticated immunocytochemical techniques for tissue localization of peptides, it became apparent that many of these peptides were contained within the nerves of the gut.

Numerous peptides have been found in both the brain and the digestive tract mucosa. The first of these to be isolated was substance P, which in the GI tract stimulates intestinal motility and gallbladder contraction. The only other peptide isolated from both the brain and gut and known to have an identical structure in both sites is neurotensin. Neurotensin increases blood glucose by stimulating glycogenolysis and glucagon release and inhibiting insulin release. Other peptides have been isolated from one site and identified by radioimmunoassay in the other. These include motilin, CCK, and VIP, which were first isolated from the gut. Enkephalin, somatostatin, and thyrotropin-releasing factor were first isolated from the brain and later found in the gut. Gastrin, VIP, somatostatin, and enkephalin also are present in the nerves of the gut.

Three peptides have important physiologic functions in the gut as neurocrines (listed in Table 1-5). Originally investigators thought that VIP was found in gut endocrine cells, but VIP is now known to be localized within the gut exclusively within nerves. It physiologically mediates the relaxation of GI smooth muscle. Smooth muscle is innervated by VIP-containing fibers, and VIP is released during relaxation. VIP relaxes smooth muscle, and VIP antiserum blocks neurally induced relaxation. In addition, strong evidence indicates that VIP physiologically mediates relaxation of smooth muscle in blood vessels and thus may be responsible for vasodilation. Besides these effects, VIP has many of the actions of its relatives, secretin and GIP, when it is injected into the bloodstream. It stimulates pancreatic secretion, inhibits gastric secretion, and

TABLE 1-5
Neurocrines

Peptide	*Location*	*Action*
VIP	Mucosa and muscle of gut	Relaxation of gut smooth muscle
GRP or bombesin	Gastric mucosa	↑Gastrin release
Enkephalins	Mucosa and muscle of gut	↑Smooth muscle tone

GRP, gastrin-releasing peptide; VIP, vasoactive intestinal peptide; ↑, stimulates.

stimulates intestinal secretion. Many of the effects of VIP on smooth muscle are mediated by nitric oxide (NO); VIP stimulates the synthesis of this potent smooth muscle relaxant.

Numerous biologically active peptides have been isolated from amphibian skin and later found to have mammalian counterparts. One of these, called *bombesin* after the species of frog from which it was isolated, is a potent releaser of gastrin. The mammalian counterpart of bombesin is gastrin-releasing peptide (GRP), which has been found in the nerves of the gastric mucosa. GRP is released by vagal stimulation and mediates the vagal release of gastrin. Luminal protein digestion products may also stimulate gastrin release through a GRP-mediated mechanism.

Two pentapeptides isolated from pig and calf brains activate opiate receptors and are called *enkephalins.* They are identical except that the C-terminal amino acid is methionine in one and leucine in the other. These compounds are present in nerves within both the smooth muscle and the mucosa of the GI tract. Opiate receptors on circular smooth muscle cells mediate contraction, and leuenkephalin and metenkephalin cause contraction of the lower esophageal, pyloric, and ileocecal sphincters. The enkephalins function physiologically at these sites and also may be an intricate part of the peristaltic mechanism. The effect of opiates on intestinal motility is to slow transit of material through the gut. These peptides also inhibit intestinal secretion. The combination of these actions probably accounts for the effectiveness of opiates in treating diarrhea.

Absent from Table 1-5 is pituitary adenylate cyclase–activating peptide (PACAP), the newest member of the secretin family. If somatostatin is blocked, injection of PACAP stimulates the release of histamine from ECL cells and therefore stimulates acid secretion. PACAP also stimulates ECL cell growth, so its actions are similar to those of gastrin. It may be a significant neural mediator of ECL cell function, but direct evidence that ECL cells are innervated by PACAP-containing fibers is missing.

PARACRINES

Paracrines are like hormones in that they are released from endocrine cells. They are similar to neurocrines because they interact with receptors close to the point of their release. The biologic significance of an endocrine can be assessed by correlating physiologic events with changes in blood levels of the hormone in question. Because the area of release of both paracrines and neurocrines is restricted, no comparable methods are available for proving the biologic significance of one of these agents. Current experiments examine the effects of specific pharmacologic blockers or antisera directed toward these substances. In vitro perfused organs are also useful in examining paracrine mediators. These systems allow an investigator to collect and assay small volumes of venous perfusate for the agent in question.

One GI peptide, somatostatin, functions physiologically as a paracrine to inhibit gastrin release and gastric acid secretion. Somatostatin was first isolated from the hypothalamus as a growth hormone release–inhibitory factor. It has since been shown to exist throughout the gastric and duodenal mucosa and the pancreas in high concentrations and to inhibit the release of all gut hormones. Somatostatin mediates the inhibition of gastrin release occurring when the antral mucosa is acidified. Somatostatin also directly inhibits acid secretion from the parietal cells and the release of histamine from ECL cells. These are important physiologic actions of this peptide.

Histamine is a second important paracrine agent. Produced in ECL cells by the decarboxylation of histidine, histamine is released by gastrin and then stimulates acid secretion from the gastric parietal cells. Histamine also potentiates the action of gastrin and ACh on acid secretion. This is why the histamine H_2 receptor–blocking drugs, such as cimetidine (Tagamet) and ranitidine (Zantac), are effective inhibitors of acid secretion regardless of the stimulus. Although parietal cells respond directly to gastrin, released histamine accounts for most of the stimulation of acid secretion by this hormone.