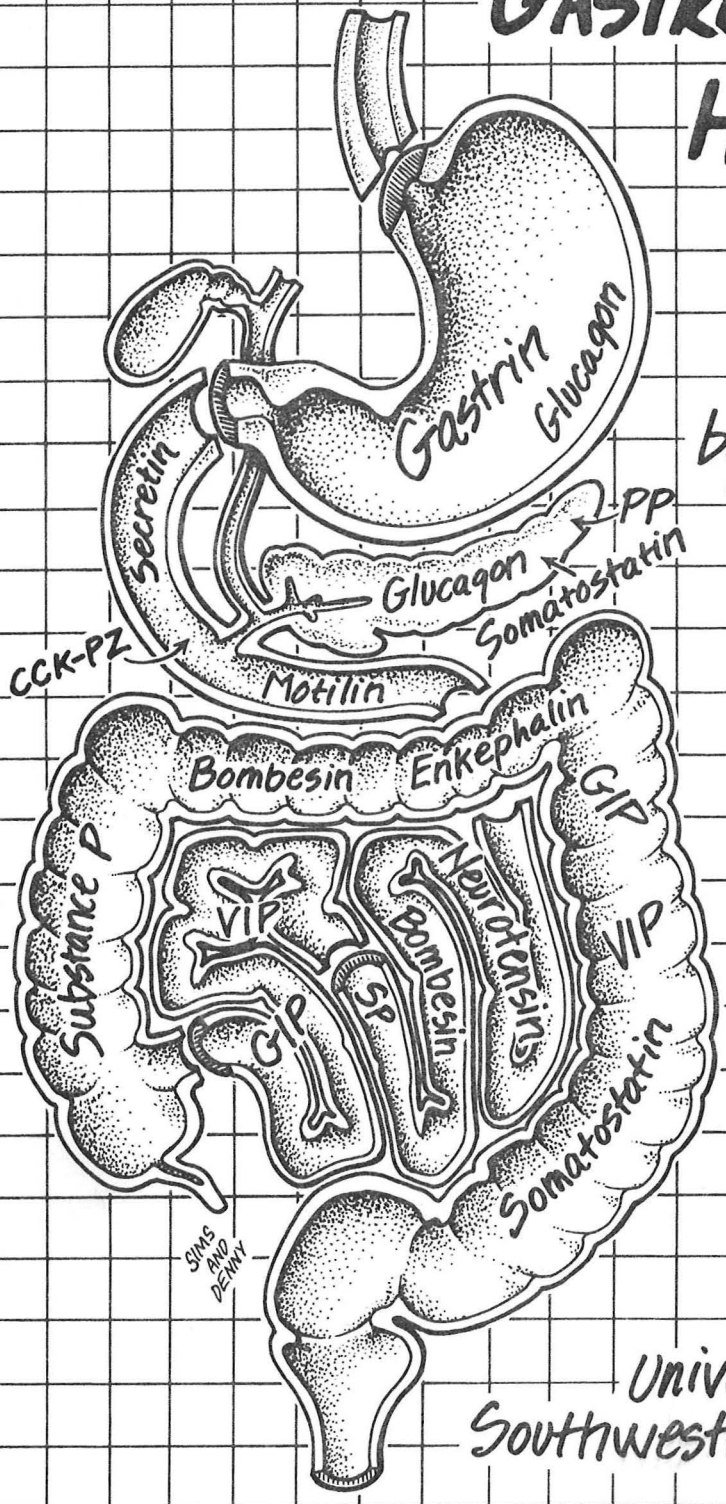
Medical Grand Rounds - May 25, 1978

GASTROINTESTINAL HORMONES



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GLOSSARY

ACTH - Corticotropin (adrenocorticotropic hormone)

AMP - Adenosine monophosphate

APUD - Amine precursor uptake and decarboxylation

CCK, CCK-PZ - Cholecystokinin-pancreozymin

EC - Enterochromaffin

EG - Enteroglucagon

GI - Gastrointestinal

GIP - Gastric-inhibitory polypeptide

LES - Lower esophageal sphincter

MEA - Multiple endocrine adenomatosis

MSH - Melanocyte-stimulating hormone (melanotropin)

PP - Pancreatic polypeptide

PZ - Pancreozymin

RIA - Radioimmunoassay

SP - Substance P

STM - Standard test meal

VIP - Vasoactive intestinal polypeptide

WDHH (or WDHA) - Watery diarrhea, hypokalemia and hypochlorhydria (or achlorhydria)

Z-E syndrome - Zollinger-Ellison syndrome

I INTRODUCTION

The recent discovery and characterization of gastrointestinal peptides have been made possible through advances in the science and techniques of peptide separation, purification, structure determination and synthesis. Our growing understanding of the role of these peptides in physiology and disease is due, in large measure, to the use of radioimmunoassay (RIA), which permits measurement of minute concentrations of hormones in blood and tissues.

The past few years have witnessed an increasing interest in gastrointestinal hormones, evidenced by a large number of national and international symposia and by published reviews dealing with the subject.[1-10] This monograph focuses on the physiologic and pathologic significance of gastrointestinal hormones in man.

II HISTORICAL BACKGROUND

Though not commonly thought of as an endocrine organ, the gastrointestinal tract is the source of numerous hormones and may well be the largest endocrine organ in the body.

It was the discovery of *secretin* by Bayliss and Starling (1902) that led to the coining of the term "*hormone*" to describe a chemical messenger that is released by one organ into the circulation to act on another organ. Isolation of pure secretin eluded many attempts and was accomplished, only 59 years later, by Jorpes and Mutt. Soon after the discovery of secretin, Edkins (1905), postulated the existence of an antral hormone, *gastrin*, that would act on the stomach to stimulate the production of gastric secretion. This discovery was challenged for years, owing largely to the difficulty of isolating the hormone and the belief that the ubiquitous histamine, also a stimulant of gastric

secretion, could be responsible for the postulated hormonal effect. All doubt about the existence of gastrin was eliminated in 1964, when Gregory and Tracy isolated the hormone from porcine antrum.

The presence in duodenal mucosa of a hormone that is distinct from secretin, is liberated by food (especially fat) and causes contraction and emptying of the gallbladder (*cholecystokinin, or "CCK"*) was discovered in 1928 by Ivy and Oldberg. Harper and Raper (1943) discovered and later partially purified a duodenal substance that stimulated the output of pancreatic enzymes. This substance, named *pancreozymin*, or "PZ", was also shown to have gallbladder-contracting activity. Jorpes and Mutt subsequently established that CCK and PZ were the same hormone (often referred to simply as CCK), which they prepared in pure form.

Additional hormones and hormone-like substances have been found in the gastrointestinal tract; these include:

1. *Gastric-inhibitory polypeptide (GIP)*, discovered in crude preparations of CCK on the basis of its inhibition of H^+ and pepsin secretion and motor activity of antral and fundic pouches.
2. *Vasoactive intestinal polypeptide (VIP)*, discovered during the search for a vasodilator peptide in tissue extracts.
3. *Motilin*, discovered following the observations that alkali in the duodenum and crude duodenal extracts produce a factor stimulating gastric motility.
4. A peptide apparently identical to pancreatic *glucagon*, found in the stomach and upper small intestine. This peptide is distinct from the glucagon-like material (enteroglucagonoid) previously discovered in intestinal extracts.
5. *Bombesin*, first discovered in the skin of the frog *Bombina bombina*, recently shown to exist in the mammalian gastrointestinal tract.

6. *Pancreatic polypeptide (PP)*, discovered during the isolation of insulin from avian pancreas, and later found in mammalian species.

7. A group of peptides known to occur in brain and other nervous tissues, discovered in intestine, pancreas or both. These include *somatostatin*, the *enkephalins* and *neurotensin*. Other peptides that first were found in the gut have now been discovered, through radioimmunoassay and immunofluorescence, to be present in the brain; these include VIP, gastrin and CCK (or peptides that are immunologically related to them). Since its discovery, *Substance P (SP)* has been known to exist both in brain and intestine.

III ORIGIN AND NATURE OF GI HORMONES: NEUROENDOCRINE SECRETION AND RELEASE OF PEPTIDES

Specific cells have been discovered in the gastrointestinal tract and pancreas that are responsible for secreting each of the above mentioned peptides. These cells have been identified by cytochemical and ultrastructural techniques, especially immunofluorescence, which depends on the use of a specific antibody against the particular peptide; interaction between the peptide (antigen) and antibody, in the presence of appropriate markers, results in fluorescence at the site of the peptide. The distribution of these specific cells is outlined in Figure 1.

All specialized peptide-secreting cells have in common a number of ultrastructural and cytochemical features, some of which reflect the ability of these cells to synthesize and metabolize biogenic amines. These characteristic features (*A*mine *P*recursor *U*ptake and *D*ecarboxylation earned the cells the acronym *APUD* and led Pearse to propose the hypothesis that cells that exhibit these properties, despite their disparate locations, have in common

important developmental and functional characteristics, including the ability to secrete peptide hormones.[11] Initially thought to arise from the neural crest, the cells are now believed to originate from neuroendocrine-programmed embryonic cells (ectoblasts); i.e., to belong to the *neuroendocrine system*.

The notion of a common neuroendocrine origin of all GI hormones helps explain the fact that some of these hormones co-exist in endocrine cells in the gut and in neural tissue of the central and autonomic nervous systems. This view accords well with the concept of *neurosecretion*, first advanced by B. and E. Scharrer in the 1940s, in relation to neurons with combined neuronal and endocrine properties.[12] These concepts underscore the functional relatedness and complementary nature of "conventional" hormones -- which must reach their target organs through the blood stream -- and neurotransmitters and other products of neurosecretion -- which can exert their influence independently of the circulation. The latter substances sometimes are referred to as "neurocrine" or "paracrine" secretions. The combined effects of these two groups of "hormonal" secretions determine the physiologic environment and characterize the true function of these peptides.[13]

Although circulating hormones and paracrine or neurocrine secretions have a fundamentally common origin, the distinction between them is important, since it determines the experimental approach to these peptides and defines the criteria required to establish their physiologic status. Thus, in order to establish the horomonal relevance of a peptide, it is necessary first to establish the existence of a digestive (or interdigestive) mechanism capable of releasing the peptide into the circulation, and secondly, to establish that the circulating levels of peptide are capable of reproducing its postulated action. Blood levels are irrelevant to paracrine or neurocrine effects, which

can mimic the effects of large amounts of injected peptide.

Table 1 lists the physiologic intraluminal stimuli capable of stimulating or inhibiting the release of GI hormones; these factors will be discussed in further detail later in this paper. Chemicals that stimulate or inhibit the release of paracrine or neurocrine peptides are still undetermined.

TABLE 1 - GI HORMONE RELEASE BY INTRALUMINAL STIMULI

STIMULUS	HORMONE				
	GASTRIN	CCK	SECRETIN	GIP	ENTEROGLUCAGON
Protein	S	S		S	
Fat		S		S	S
Sugar				S	S
Acid	I		S		

Abbreviations: S-stimulates; I-inhibits; CCK-cholecystokinin-pancreozymin; GIP-gastric-inhibitory polypeptide.

IV ANATOMIC AND CELLULAR DISTRIBUTION OF GI HORMONES

The use of immunofluorescent and other cytochemical techniques, coupled with ultrastructural examination, permit the identification and characterization of the cells responsible for storing or secreting the various GI hormones. Morphologists are in general -- though not unanimous -- agreement on the nomenclature of these cells in the GI tract and the pancreas (Table 2; see Fig. 1).[9]

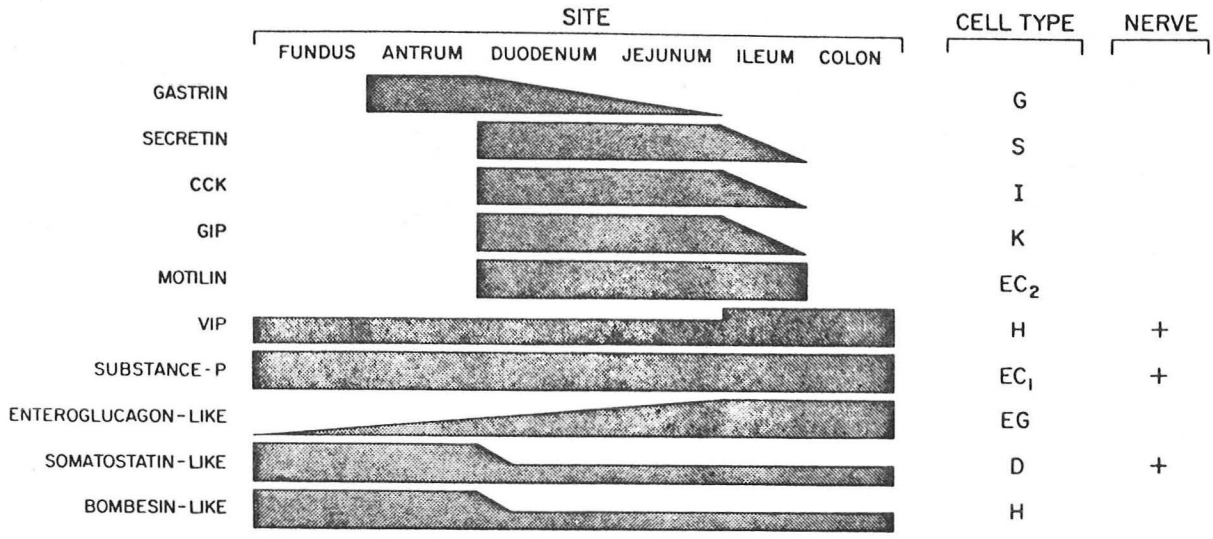

Figure 1. Anatomic and cellular distribution of GI hormones (Modified by permission; from Grossman.) Plus sign (+) signifies presence of peptides in neural site.

TABLE 2 - PANCREATIC ENDOCRINE CELLS AND THEIR SECRETIONS

Cell	LOCATIONS	SECRETION
α	Islets	Glucagon
β	Islets	Insulin
D	Mainly islets	Somatostatin
D_1	Islets and non-islets	VIP
D_2	Mainly non-islets	PP

(From Pearse *et al*[9].)

For the most part, each endocrine cell is associated with one peptide hormone, but there are exceptions; for example, (1) the same (D_1) cell may contain VIP and bombesin; (2) the localization of met-enkephalin appears to coincide with that of gastrin (G cell); and (3) the enterochromaffin (EC) cell system, consisting of at least two distinct cells, contains -- in addition to motilin or SP -- several other peptides as well as serotonin (5-hydroxytryptamine). Anatomic localization of these cells has been accomplished by morphologic examination of sections from various parts of the GI tract, often combined with RIA of tissue extracts. Certain hormones, such as gastrin and secretin, have a relatively restricted distribution, while others, such as VIP and SP, occur throughout the length of the GI tract.

V CHEMICAL AND BIOLOGICAL FEATURES OF GI HORMONES: STRUCTURE AS A GUIDE TO BIOLOGICAL ACTION

An examination of the chemical characteristics and structure of GI hormones can yield insights into their actions and possible functional interrelationships. On the basis of their amino acid composition and sequence, as well as the methods leading to their isolation from crude tissue extracts, two distinct groups of GI hormones may be identified. Each of these groups consists of hormones that are not only structurally related but that also exhibit similar biologic actions.

One group includes secretin, VIP, glucagon and, to some extent, GIP. These peptides show extensive homologies in their amino acid sequences (Fig. 2). Vasoactive intestinal polypeptide and secretin are purified together from intestinal extracts, beginning with the same crude fraction, almost to the final steps. Peptides in this group also share important activities. Thus, secretin and VIP relax GI and other smooth muscle and stimulate pancreatic

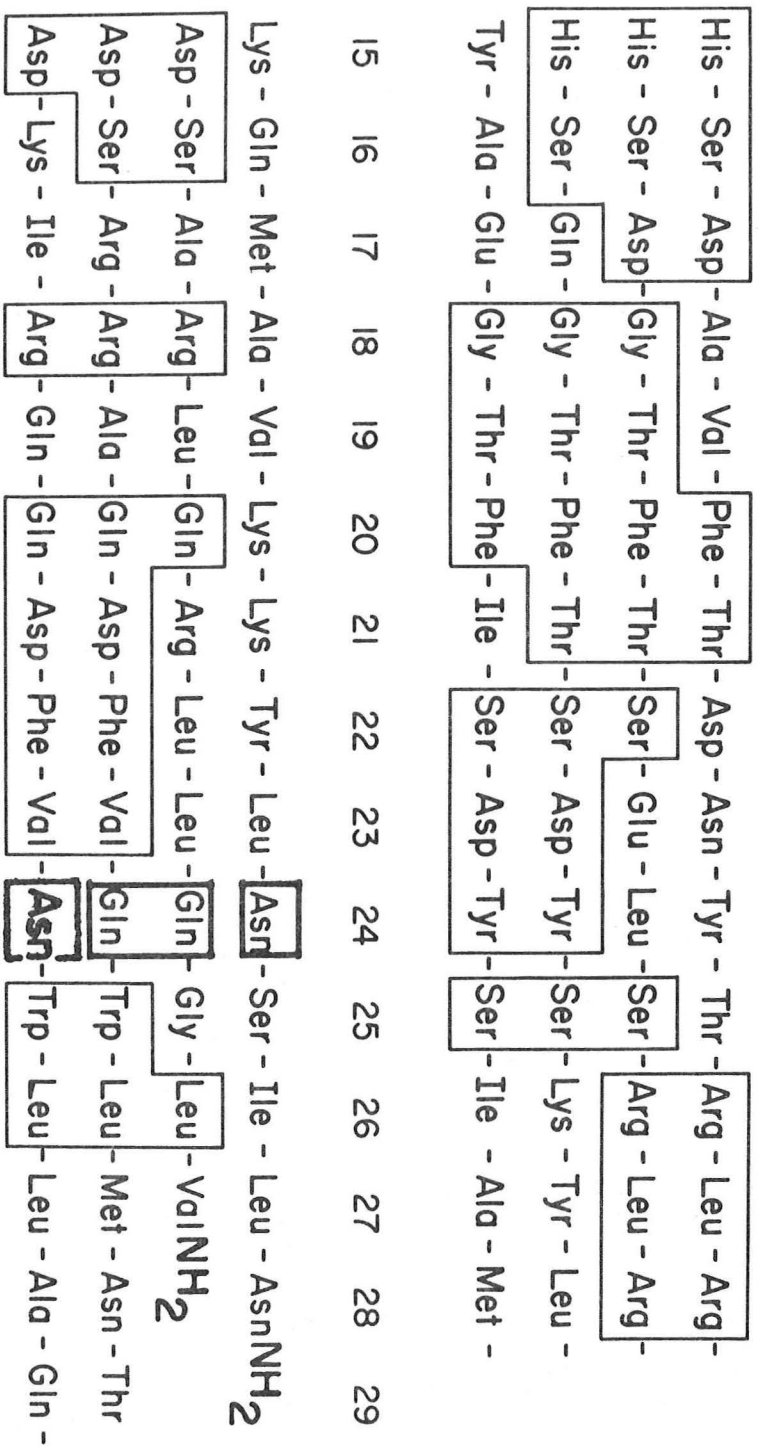

Figure 2. Amino-acid sequence of porcine VIP, secretin, glucagon and GIP. Identities between two or more of the peptides are framed. (NH_2 = amide group at C-terminal end of VIP and secretin).

water and bicarbonate secretion; glucagon and VIP stimulate glycogenolysis and myocardial contractility; GIP and VIP inhibit gastric acid secretion and stimulate insulin secretion; and VIP, glucagon and GIP stimulate intestinal juice secretion.

Another group includes the gastrins, CCK-PZ and, to some extent, GIP, which is purified from crude preparations of CCK-PZ. Chemical similarities between the gastrins and CCK-PZ are striking. The C-terminal 5-peptide (Gly-Trp-Met-Asp-Phe-NH_2) is identical (Fig. 3), and both contain a sulfated tyrosine residue in the C-terminal 7-peptide (directly linked to the C-terminal 5-peptide in gastrin but separated by a methionine residue in CCK). In both peptides the C-terminal end possesses the full range of biologic activity. The C-terminal 8-peptide of CCK has all the activities of the whole molecule and is even about 10 times more active; the C-terminal 4-peptide of gastrin is fully active, although 10% as potent as gastrin-17. Related to this group also are other peptides found in non-mammalian species, e.g., caerulein and bombesin isolated from amphibian skin. The former is a counterpart of mammalian gastrin and CCK-PZ, while the latter, a potent gastrin releaser, is itself present in mammalian gut. Biologic actions common to gastrin and CCK are: stimulation of gastric acid secretion, stimulation of GI smooth muscle (especially of stomach and gallbladder), stimulation of pancreatic enzyme secretion and stimulation of growth of gastric mucosa (gastrin) or of exocrine pancreas (CCK-PZ).

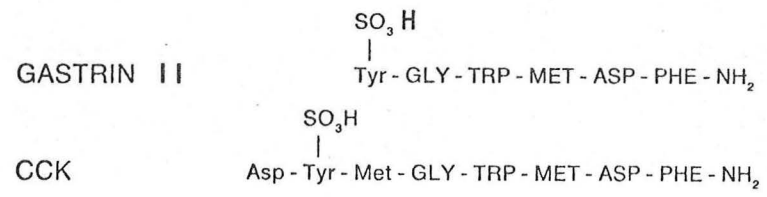

Figure 3. C-terminal sequences of gastrin II and CCK. Identities are capitalized.

It is tempting to explain the similarities between members of these hormonal families on the basis of evolutionary changes from common ancestors. Bodanszky, however, emphasizes that major (nonconservative) differences exist between members of the secretin family, and that these differences, along with corresponding evolutionary changes in hormone receptors that also must be postulated, cannot be explained by simple evolutionary schemes.[14]

VI GI HORMONES IN PHYSIOLOGY

SECRETIN[10]

Secretin (S) is contained in specialized cells located in the duodenum and jejunum.

Biological Actions: The gastrointestinal actions of secretin include stimulation of pancreatic water and bicarbonate secretion; stimulation of water and electrolyte secretion by liver (in bile); stimulation of pancreatic enzyme secretion; inhibition of gastric motility, gastric acid secretion and gastric emptying; inhibition of gastrin-stimulated contraction of the lower esophageal sphincter; stimulation of gastric pepsin secretion and, in larger doses, stimulation of insulin secretion and of lipolysis in fat cells. The full biologic activity appears to require the complete sequence of the 27-residue peptide (see fig. 2), though shorter fragments of the molecule retain certain limited actions and the ability to bind to target tissues.

Physiologic Roles: Of the above listed effects of secretin, it is likely that its main -- and perhaps only -- physiologic action is the stimulation of pancreatic water and bicarbonate secretion. This, of course, is the action that led to the discovery of secretin and the coining of the term "hormone".

It is ironic, therefore, that measurements of secretin by RIA have not documented its release into the circulation except after strong acidification (pH < 4.5) of the duodenum, an unphysiologic condition. On the other hand, RIA's that are sensitive for secretin have only recently become available, and it is entirely possible that the physiologic bicarbonate output in response to a meal is mediated by the release of small amounts of secretin (too minute to be detected by present methods), augmented by the simultaneously released CCK. These two peptides potentiate each other's effects such that in combination, relatively small doses of either can produce a maximal bicarbonate and enzyme response from the pancreas.

GASTRIN

Gastrin (G) exists in specialized endocrine cells in the pyloric gland area (antrum) of gastric mucosa and, to a lesser extent, in the duodenum and jejunum.

Molecular Forms of Gastrin in Blood and Tissues[15-18]: The gastrin first isolated by Gregory and Tracy from hog antrum consists of 17 amino acid residues (gastrin-17 or G-17). Human gastrin-17 (Fig. 4) differs only in minor respects from corresponding molecules in other mammalian species. As mentioned earlier, biologic activity resides in the carboxy-terminal tetrapeptide amide (see fig. 3). Pentagastrin (Peptavlon), a synthetic derivative of this active fragment, is used commonly to elicit the effects of gastrin in man and animals.

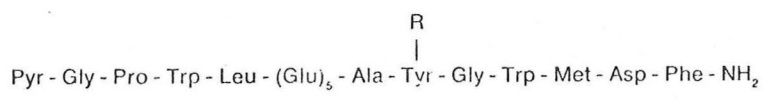

Figure 4. Amino-acid sequence of human little gastrin (G-17). Pyr = Pyroglutamyl; R = H in gastrin I, and SO3H in gastrin II.

The molecular heterogeneity of gastrin in tissue and blood was first recognized by Yalow and Berson. These investigators found that antral mucosal gastrin was mainly gastrin-17 (G-17), but that the predominant circulating gastrin after a meal was a larger, less acidic molecule (gastrin-34). Gastrin-34 (G-34) is not a dimer of G-17, but consists of the latter molecule joined at its N-terminal end with a structurally independent 17-residue peptide chain.

One reason for the abundance of G-34 in the circulation is its longer half-life (36 minutes, versus 6 minutes for G-17, in man). Gastrin-34 is about five times less potent on a molar basis than G-17 (five times greater increments in molar concentrations of serum G-34 than of G-17 are required to elicit the same rate of acid secretion). Thus, despite its abundance in the circulation, G-34 accounts for less than half of the biologic activity of gastrin in the blood. Between them, G-34 and G-17 account for 90% of immunoreactive gastrin in the blood. Other forms of gastrin include "big big gastrin" and "minigastrin" or gastrin-14, the C-terminal tetradecapeptide of G-17 (Fig. 5). There is doubt whether "big big gastrin" exists in the circulation.

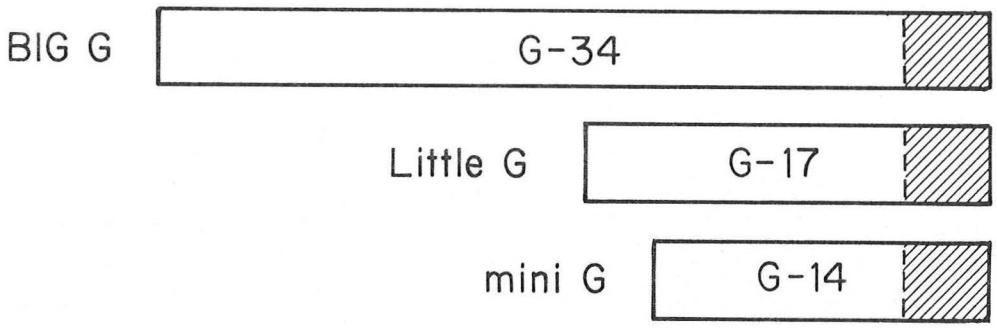

Figure 5. Molecular forms of gastrin. Shaded area represents active site (C = terminal tetrapeptide amide) common to all forms of gastrin (Modified by permission, from McGuigan and Herbst[16]).

Biologic Actions[19-22]: The actions of gastrin are diverse and include stimulation of gastric acid and pepsin secretion; stimulation of pancreatic enzyme secretion and gallbladder contraction (compare with CCK); contraction of smooth muscle of the lower esophageal sphincter and stomach; increase in gastric mucosal blood flow; stimulation of histamine synthesis and release; and stimulation of protein synthesis in gastric mucosa. In larger doses, gastrin promotes the growth of gastric mucosa, duodenal mocosa and pancreas, and stimulates the release of insulin and of calcitonin.

Release: *Chemical Influences* -- Food is the primary physiologic stimulus to gastrin release; specifically, food in the form of partly digested protein. Calcium salts in food (as in milk), but not magnesium salts, enhance gastrin release. Gastric acid secretion stimulated by gastrin release suppresses further release of gastrin; a threshold pH of 2.5, normally found after a meal, is sufficient for this purpose[22a]. Elevation of pH in the fasting stomach by ingestion of alkalis or antacids (unless given in the form of calcium salts) does not, of itself, stimulate gastrin release; however, neutralization of acid secretion by antacids enhances food-stimulated gastrin release.

Neural Influences -- Gastrin is the only gut hormone under neural control. In animals, the vagus nerve mediates gastrin release prior to and in anticipation of the ingestion of food (cephalic phase). In man, this component of gastrin release is minor. Antral distention, which activates neural reflexes, contributes minimally to gastrin release in man, though it stimulates acid secretion[22b]. In effect, vagal influences appear to be largely inhibitory in man. Support for this notion is based on the enhanced gastrin

response to food and other stimuli after surgical or medical vagotomy (atropine).

Humoral Influences -- Somatostatin-secreting (D) cells and VIP-secreting (D_1) cells are found in close proximity to gastrin-secreting (G) cells in the human antrum. Since both somatostatin and VIP inhibit gastrin release on injection, it is possible that the local (paracrine) secretion of these peptides might play a regulatory role in gastrin release. On the other hand, bombesin, which curiously is secreted by the same cell that secretes VIP, is one of the most potent stimulants of gastrin release. The presence in one cell of two peptides with opposite effects (though bearing some structural similarity to each other) suggests more complex forms of humoral regulation. Secretin normally inhibits gastrin release, but stimulates it in patient with gastrinoma (see later section).

Physiologic Effects: In man, the physiologic effects of gastrin probably are stimulation of gastric acid (and pepsin) secretion; increase of gastric mucosal blood flow; and stimulation of GI mucosal growth (trophic action). It is doubtful that gastrin exerts a physiologic action on the lower esophageal sphincter (this point is discussed in greater detail later).

Post-prandial blood levels of gastrin are two- or threefold above fasting levels and, as mentioned above, the measured immunoreactive gastrin is mainly G-34. Circulating levels may be increased in a number of pathologic states; the causes and differential diagnosis of these conditions are discussed later in this paper.

CHOLECYSTOKININ-PANCREOZYMIN (CCK-PZ or CCK)[10]

Biologic Activity and Relationship to Gastrin: Cholecystokinin-pancreozymin is a 33-residue peptide (Fig. 6) present in specialized (I) cells in the upper small intestine. We have already commented on the striking

similarity between the C-terminal ends of CCK and of gastrin (see Fig. 3). An important distinguishing feature between the two peptides is the location of the sulfated tyrosine residue; in CCK at position 7, and in gastrin at position 6, counting from the C-terminus. This structural difference accounts for the characteristic biologic effects of CCK on pancreatic enzyme secretion and gallbladder contraction. Also, unlike the gastrins, which occur naturally in sulfated (gastrin II) or unsulfated (gastrin I) forms, CCK is always sulfated; desulfation of CCK results in loss of its biologic activity.

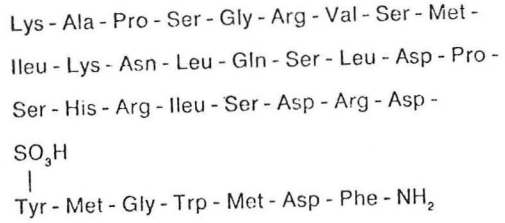

Figure 6. Amino-acid sequence of porcine CCK-PZ.

A variant of CCK consisting of 39 amino acid residues is also known to exist, but it is not known whether CCK circulates in more than one form. Studies of blood and tissue CCK levels and molecular forms have been hampered by the difficulty in iodinating the sulfated tyrosine residue and the scarcity of pure CCK needed as label and as reference standard in the assay.

Normal Release: Although absolute blood levels of CCK are difficult to ascertain, it is clear that a significant increment in CCK immunoreactivity occurs in the blood after a solid meal or milk (one pint). Because the intraluminal stimulus that leads to the rise in blood levels in physiologic, it can be assumed reasonably that CCK is a true hormone that acts on its

release into the circulation. Perfusion of the proximal intestine with fat, partly digested protein or essential amino acids elicits contraction of the gallbladder and stimulation of pancreatic enzyme secretion in man and animals, consistent with the release of CCK-like activity from the intestine. In such experiments, however, the concentration and amount of perfusate are often unphysiologic in the sense that they are not normally attained in the lumen of the intestine.

The relationship between blood levels and biologic activity cannot be examined fully until it becomes possible to identify the nature of circulating molecular form(s) of CCK and their respective potencies.

Physiologic Effects: In man, these include stimulation of pancreatic enzyme secretion and gallbladder contraction, and potentiation of the action of secretin on pancreatic electrolyte secretion. (As discussed above, secretin, in its turn, potentiates the effect of CCK on pancreatic enzyme secretion). Cholecystokinin-pancreozymin also inhibits gastric emptying of fluids in the dog at doses that are below those required to produce half-maximal secretion of pancreatic enzymes. It is unknown whether this effect applies in man.

Although pyloric sphincter muscle is highly sensitive to CCK *in vitro* and the intact pyloric sphincter in man contracts after intravenous injection of CCK, it is uncertain whether this effect is truly physiologic. It is worth noting in this context that the effects of CCK on gastric emptying and pyloric function would be cooperative since it is now thought that the emptying of gastric fluid is regulated by the gastric musculature, whereas the emptying of solids and the prevention of reflux of duodenal contents is controlled by the pyloric sphincter.

GASTRIC-INHIBITORY POLYPEPTIDE (GIP)[23]

This 43-residue polypeptide, which bears structural similarities to glucagon and secretin (see Fig. 2), was given its name because of its inhibitory activity on gastric acid secretion and motility. Gastric-inhibitory polypeptide has also been found to have a potent insulin-releasing effect that depends on the presence of glucose; the term "GIP" thus may refer also to the *glucose-dependent insulinotropic peptide*. Like secretin and CCK, GIP occurs in the upper small intestine, being located in specialized (K) cells.

Actions, Release and Function: Gastric-inhibitory polypeptide is released into the blood stream by fat, glucose and a mixed meal. The GIP release provoked by oral glucose is accompanied by a rise in serum insulin levels, and the degree of insulin release is related to the amount of glucose ingested. The insulinotropic effect of GIP can be reproduced by the intravenous infusion of GIP together with glucose. Ingestion of triglycerides also increases GIP and insulin levels in the blood, but the insulinotropic effect requires a minimal increment of glucose (20 mg/dl). Although triglycerides also release CCK from the small intestine, the effect of this peptide on insulin release is temporary. Like CCK, other gastrointestinal peptides (secretin, gastrin) can produce insulin release on intravenous administration, but their effect, unlike that of GIP, is short-lived. It appears, therefore, that the main physiologic action of GIP is its glucose-dependent insulinotropic effect. The role of GIP in the post-prandial suppression of gastric acid secretion and motility ("enterogastrone" effect) is still uncertain.

MOTILIN[24]

This 22-residue peptide is present in the small intestine, located in enterochromaffin (EC_2) cells that are similar to but distinguishable from EC_1 cells, which contain substance P (Fig. 7). Motilin does not show clear structural similarity to any other GI hormone.

1	2	3	4	5	6	7	8	9	10	11
Phe	Val	Pro	Ileu	Phe	Thr	Tyr	Gly	Glu	Leu	Gln
12	13	14	15	16	17	18	19	20	21	22
Arg	Met	Gln	Glu	Lys	Glu	Arg	Asn	Lys	Gly	Gln

Figure 7. Amino-acid sequence of porcine motilin.

Actions: In dogs, motilin stimulates motor activity of the gastric fundus and enhances gastric emptying of liquids. This action appears to depend on the presence of vagal tone. Infusions of motilin also increase the frequency of inter-digestive myoelectric activity -- a series of propagated contractions which, between meals, flush the stomach and small bowel of their contents. In man, intravenous infusions of the synthetic 13-norleucine peptide have been reported to induce contraction of the lower esophageal sphincter, stimulation of pepsin secretion, delay of gastric emptying and reduction of gastric mucosal protein synthesis.

A physiologic role for motilin remains uncertain. The stimulus originally believed to elicit its release in dogs, i.e., alkalinization of the duodenum (to pH 10), is probably unphysiologic. In man, release of the peptide appears to be provoked by acid, not alkali, in the duodenum.

GLUCAGON, ENTERGLUCAGON

It has been known for some time that the intestine, especially the ileum and the colon, contains glucagon-like immunoreactive material (enteroglucagon).

This material, which has not yet been fully purified, is present in specialized (EG) cells.

Recently, Unger and co-workers have reported the occurrence in canine stomach of a peptide that is indistinguishable, biologically and immunologically, from pancreatic glucagon. This gastric glucagon is located in α cells, much like the pancreatic islet cells by the same designation. In the human stomach, the glucagon content appears to be low, and α cells, sparse[25].

The physiology of gut glucagon should be considered as a part of the overall physiology of glucagon. This subject has been fully covered in a recent review[26].

PANCREATIC POLYPEPTIDE (PP)

This 36-amino acid residue peptide (Fig. 8) is present almost exclusively in the pancreas, in D_2 cells, located throughout the exocrine pancreas. A few of these cells are found in the islets and in the stomach and upper small intestine. First isolated in chicken pancreas, this peptide also has been purified from the pancreas of several mammalian species, including man.

1	2	3	4	5	6	7	8	9	10	11	12	13	14
Ala	Pro	Leu	Glu	Pro	Val	Tyr	Pro	Gly	Asp	Asn	Ala	Thr	Pro
15	16	17	18	19	20	21	22	23	24	25	26	27	28
Glu	Gln	Met	Ala	Gln	Tyr	Ala	Ala	Asp	Leu	Arg	Arg	Tyr	Ileu
29	30	31	32	33	34	35	36						
Asn	Met	Leu	Thr	Arg	Pro	Arg	Tyr	NH_2					

Figure 8. Amino-acid sequence of human pancreatic polypeptide. (Personal communication, Dr. Ronald E. Chance, Eli Lilly Laboratories.)

Actions and Release: In the dog, bovine PP stimulates basal gastric acid secretion, but inhibits pentagastrin-stimulated acid secretion. In small doses, the peptide also relaxes the gallbladder, increases the tone of the bile duct and inhibits pancreatic enzyme secretion.

The biologic actions of human PP have not been investigated. Though PP is released into the circulation after food intake, its possible physiologic role is, at present, unknown. Since bombesin also is released after a mixed meal and is a potent stimulant of PP release, it has been suggested that bombesin may regulate the release of PP.

VASOACTIVE INTESTINAL POLYPEPTIDE (VIP)[27-30]

Distribution[31-33]: Vasoactive intestinal polypeptide, originally discovered and isolated from porcine duodenum on the basis of its vasodilator actions, is now known to exist more widely in normal tissues and to have a broader range of actions than its name implies. Although many organs, especially brain and nervous tissues from mammalian and non-mammalian species, have been found to contain VIP-like immunoreactivity (by RIA and immunofluorescence), full isolation of the peptide from these additional sites has not been carried out. In the GI tract, VIP is present from the esophagus to the rectum, as well as in the pancreas. It is localized in endocrine cells (D_1) and in nerves, being richest in Meissner's and Auerbach's plexuses.

Biologic Actions: Vasoactive intestinal polypeptide has a wide spectrum of biologic actions, as outlined in Table 3. Some of the recently reported actions include (1) binding to specific receptors and stimulation of cyclic adenosine monophosphate (AMP) production, in near-physiologic doses, in isolated enterocytes from rat small intestine; (2) stimulation of adenylate

cyclase activity and of secretion in rat colon, as in ileum and jejunum of other species; (3) stimulation of membrane receptors in pancreatic acinar cells from guinea pigs; (4) stimulation of insulin, glucagon and somatostatin secretion in the perfused cat pancreas; (5) relaxation of the lower esophageal sphincter in the anesthetized opossum and the awake baboon; (6) prevention of the bronchoconstrictor effect of prostaglandin $F_{2\alpha}$ or histamine in dogs; (7) augmentation of internal carotid blood flow in anesthetized dogs; and (8) arousal, demonstrated by electroencephalography during sleep, in anesthetized dogs. Many of these effects have been confirmed recently in human subjects.

TABLE 3 - BIOLOGIC ACTIONS OF VIP

Cardiovascular System:	Vasodilation (peripheral, splanchnic, coronary); hypotension; moderate inotropic effect.
Respiratory System:	Bronchodilation; augmented ventilation
Gastrointestinal System:	
Esophagus	Relaxation of lower sphincter
Stomach	Relaxation; suppression of acid and pepsin secretion
Pancreas, liver	Stimulation of water and bicarbonate secretion; increased bile flow
Gallbladder	Relaxation
Small Intestine	Stimulation of water and ion secretion
Large Intestine	Relaxation, stimulation of water and ion secretion
Metabolism:	Increased glycogenolysis; hyperglycemia; insulin and glucagon release; lipolysis; stimulation of adenylate cyclase
Central Nervous System:	Arousal

VIP in Nervous System Tissues: The highest concentrations of VIP in brain are in the cerebral cortex, hypothalamus, amygdaloid nucleus and corpus striatum. In these locations immunocytochemical techniques localize the peptide in nerve terminals and neurons. Subcellular fractionation of cerebral cortex, hypothalamus and corpus striatum reveals the highest concentrations of the peptide in synaptosomal fractions (isolated presynaptic nerve terminals). The polypeptide also is found in the peripheral autonomic nervous system, especially in (1) the superior and inferior mesenteric ganglia; (2) the submucous (Meissner's) and myenteric (Auerbach's) plexuses of the intestinal wall; (3) cerebrovascular nerves; and (4) nerves in the female and male genital organs.

VIP in Placenta[34]: Human placenta contains immunoreactive VIP in concentrations that are at least two orders of magnitude higher than those in peripheral venous blood, and VIP levels of cord blood are about three times as high as in normal plasma. The placenta has also been found to be rich in gastrin immunoreactivity.

Possible Physiologic Roles: Although the possible physiologic role or roles of VIP are still unknown, the following speculations are suggested by data outlined above:

1. The selective localization of VIP within the nervous system, its concentration in synaptosomal preparations and its release from synaptosomes with depolarizing stimuli (e.g., high K^+ concentrations) suggest that VIP may serve as a neurotransmitter or neuromodulator, both in the central nervous system and in the peripheral autonomic system.[35]
2. The peptide may mediate vasodilation in several vascular beds, including

the splanchnic circulation.

3. VIP may participate in the regulation of gastrointestinal motor tone, motility and secretion. The findings that VIP stimulates intestinal cyclic AMP production in physiologic doses, and that the intestinal VIP content in rats rises sharply between the second and ninth weeks after birth, are in keeping with a such a regulatory role.

SOMATOSTATIN[36]

Somatostatin, or growth hormone release-inhibiting hormone, is a 14-residue peptide (Fig. 9) that was first isolated from the hypothalamus. Since then, it has been found in other parts of the brain and, more recently, in the gut (where the highest concentrations are in the gastric antrum, and progressively decreasing concentrations are found in the small intestine and colon) and the pancreas (where it is localized in nerves and in the D cells).

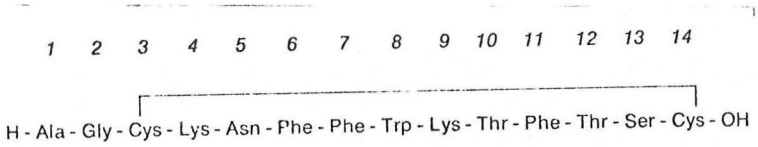

Figure 9. Amino-acid sequence of somatostatin.

Actions: In addition to inhibiting the release of growth hormone, somatostatin inhibits the release of insulin, glucagon, gastrin (even in cases of gastrinoma), secretin and VIP (in VIP-secreting tumors). It also suppresses gastric acid and pancreatic enzyme secretion, gastric emptying, gallbladder contraction and duodenal motility, and intestinal carbohydrate absorption, and reduces splanchnic and gastric mucosal blood flow.

Function: Achieved on injection, these powerful and sweeping actions are unlikely to be exercised in the normal state, where the GI effects of the peptide may be limited to local (paracrine) control of other endocrine and exocrine secretions.

SUBSTANCE P (SP)

An 11-residue peptide (Fig. 10), SP, was discovered in the brain and intestine more than 46 years ago, but only recently was isolated, chemically characterized and synthesized. The peptide occurs widely -- but selectively -- in the brain and spinal cord. On subcellular fractionation of nervous system tissue, SP, like VIP, is concentrated in the synaptosomal fraction. In the GI tract, SP is localized in intramural nerve plexuses and in endocrine cells in the intestinal mucosa, identified as enerochromaffin (EC_1) cells, which also harbor serotonin.

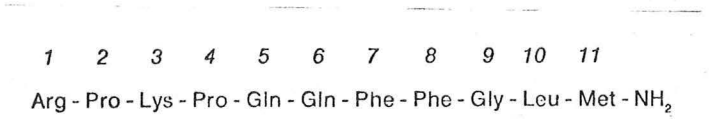

Figure 10. Amino-acid sequence of Substance P.

The actions of SP include systemic vasodilation; contraction of most non-vascular smooth muscle; stimulation of salivary secretion; and histamine release. Much useful information on SP has been summarized in a recently published monograph.[37]

BOMBESIN[38]

One of a large group of biologically active peptides isolated from amphibian skin, but also thought to occur in the mammalian GI tract, this 14-residue peptide (Fig. 11) has potent activities on GI function. These

include stimulation of gastric acid secretion; contraction of gallbladder; relaxation of the choledochoduodenal junction; and stimulation of pancreatic secretion that is rich in protein and poor in bicarbonate. These effects are caused by the stimulated release of gastrin and of CCK. Bombesin has additional actions, including complex effects on myoelectric activity of the GI tract, contraction of non-vascular smooth muscle, and antidiuresis. The possible physiologic significance of this peptide in man is, at present, unknown. Bombesin-like immunoreactivity has been found in the same mucosal endocrine cells (D_1) that contain immunoreactive VIP; despite their different actions, the two peptides show certain structural similarities.

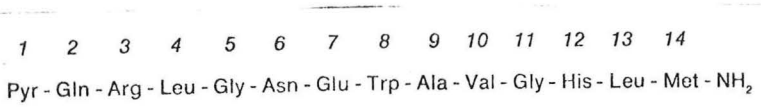

Figure 11. Amino-acid sequence of bombesin.

OTHER PEPTIDES

Other GI peptides with interesting biologic actions but with still unknown physiologic significance or incompletely defined chemical structure include bulbogastrone, chymodenin, coherin, enkephalins, neurotensin and urogastrone (probably identical to epidermal growth factor).

VII GI HORMONES IN DISEASE

HORMONE-SECRETING TUMORS[39-42]

With the exception of carcinoid tumors, most endocrine tumors of the GI system originate in pancreatic islets. Islet cell tumors may secrete hormones that are normally produced there (see Table 2), including glucagon, insulin, somatostatin, VIP and PP. In addition, these tumors also may secrete hormones that are not normally secreted by the islets such as gastrin

and, less commonly, ACTH and melanocyte-stimulating hormone (MSH). Some islet cell tumors secrete more than one hormone, although the effects of one hormonal secretion usually predominate. Such effects are often dramatic even though the tumors themselves may be very small. Some of the clinical syndromes associated with islet-cell tumors, and the hormonal substances that mediate these syndromes (Table 4), are discussed below.

TABLE 4 - ISLET CELL TUMORS

SYNDROME	HORMONAL MEDIATOR
Z-E	Gastrin
Pancreatic cholera (Werner-Morrison, WDHH)	VIP
Glucagonoma	Glucagon
Somatostatinoma	Somatostatin
Insulinoma	Insulin

The Zollinger-Ellison (Z-E) Syndrome (Ulcerogenic Islet Cell Syndrome, Gastrinoma)[39-43]: In 1955, Zollinger and Ellison reported the association of severe peptic ulcer disease, marked gastric acid hypersecretion and islet cell adenoma or adenocarcinoma. They concluded that the pancreatic tumors produced a "potent gastric secretagogue" that was "responsible for the acid hypersecretion and the fulminating ulcer diathesis"; this secretagogue since has been identified as gastrin.

Analysis of 1000 cases of gastrinoma that have been compiled through a special registry* reveals that the ulcers may be chronic and otherwise

*Kept by Dr. Stuart D. Wilson, Medical College of Wisconsin, Milwaukee. Both Dr. Wilson and Dr. Zollinger estimate that many cases of the Z-E syndrome are no longer being reported (personal communication).

unremarkable, or may present special features such as multiple and unusual (e.g., jejunal) locations; complications (e.g., penetration , perforation or hemorrhage); resistance to conventional medical treatment; and recurrence after simple surgical procedures.

The acid hypersecretion characteristically is present even under basal conditions, and consequently basal acid output often is 60% or more of peak (maximal, histamine-stimulated) acid output. Gastric hypersecretion and mucosal hypertrophy often are reflected on roentgenographic examination as enlargement of the stomach and exaggeration of gastric folds and small bowel rugae (reminiscent of Menetrier's syndrome). The persistent hypersecretion of gastric acid also may cause chronic diarrhea and steatorrhea, attributable to the large volumes of acid reaching the duodenum, stimulating intestinal secretion, impairing small intestinal absorption of water and electrolytes, and inactivating pancreatic lipase. Continuous suction of gastric contents alleviates the diarrhea. The H_2-receptor blockers, cimetidine & metiamide -- potent inhibitors of acid secretion but not of tumor gastrin release -- also relieve the diarrhea.

The serum gastrin levels in gastrinoma often are elevated markedly: usually greater than 1000, and sometimes higher than 10,000 or even 100,000 pg per ml (normal levels are less than 100-200 pg per ml).

Other Causes of Gastrinemia[44]: In addition to gastrinoma, other conditons may be associated with gastrinemia (Table 5). These include pernicious

anemia and chronic atrophic gastritis, two conditions associated with decreased or absent gastric acid; massive resection of small intestine (short bowel syndrome); retained antrum syndrome; and antral G-cell hyperplasia, conditions characterized by increases gastric acid secretion. These non-tumorous causes of gastrinemia and hyperchlorhydria need to be distinguished from gastrinoma, especially when blood gastrin levels are not extremely high (1000 pg per ml). The differential diagnosis is based on the differential responses of gastrin levels to the provocative stimuli of a standard test meal (STM), and injections of secretin and of calcium (Table 6). Patients with the Z-E syndrome respond minimally to STM since most of their gastrin comes from the tumor, but are hyperesponsive to secretin and calcium; the response to secretin (1-2 units per kg) reaches a peak two to fourfold increase within 10 minutes, returning to pre-injection levels within 30-60 minutes. The calcium provocation test should be avoided in patients with hypercalcemia (see section below on multiple endocrine adenomatosis). Conversely, gastrin levels in patients with non-tumorous hypergastrinemic hyperchlorhydria rise markedly in response to a meal (well above the two to threefold increase in normal subjects), but not in response to secretin or calcium.

TABLE 6 - DIFFERENTIAL DIAGNOSIS OF HYPERCHLORHYDRIC HYPERGASTRINEMIA

GASTRIN LEVELS	Z-E SYNDROME	NON-TUMOROUS CAUSES
Fasting	Often >1.0 ng/ml	Usually <1 ng/ml
Response to STM	Slight	Pronounced
Response to secretin	Two-to fourfold rise within 10 min	No change or fall
Response to Ca^{++}	Large, slow (3 hr) rise	Slight

In practice, patients with duodenal ulcer disease should be subjected to a basal gastric secretory test; all patients with an acid output greater than 10 mEq per hour should be examined for evidence of fasting hypergastrinemia. Patients with recurrent ulcers following operation; or ulcers associated with diarrhea, with large gastric rugal folds, with a family history of ulcers or endocrine disorders, or with other unusual features outlined above should also be examined for hypergastrinemia. All those with fasting hypergastrinemia should be subjected to the provocative tests described above.

Multiple Endocrine Adenomatosis (MEA) Syndromes[45]: In 20% - 50% of patients with gastrin-producing pancreatic tumors, there is a family history of ulcers or of other endocrine abnormalities. In such instances the Z-E syndrome may be considered part of a larger entity; that is inherited as an autosomal dominant, namely, multiple endocrine adenomatosis (MEA). In this disorder, gastrin-secreting (or other islet cell tumors usually are coupled with hyperparathyroidism and with involvement of the anterior pituitary (MEA I or Wermer's syndrome). Other expressions of MEA include pheochromocytoma, medullary thyroid carcinoma and hyperparathyroidism (MEA-II or Sipple's syndrome), and other combinations of abnormal growth of endocrine cell types. Cases of gastrinoma are on record where the islet cell tumor secreted ACTH or other hormonal products in addition to gastrin.

Watery Diarrhea Syndrome (Verner-Morrison Syndrome, Pancreatic Cholera, Diarrheogenic Islet Cell Syndrome, WDHA or WDHH Syndrome, VIP-oma): This syndrome is characterized by severe, intractable, chronic watery diarrhea with hypokalemia, hypochlorhydria (less commonly, achlorhydria) and, in some cases, hyperglycemia, hypercalcemia and episodes of flushing. The diarrhea, which is of a secretory nature, leads to marked loss of water and electrolytes

from the small and large intestine. The gallbladder often is dilated, but the GI system appears otherwise unremarkable on examination by routine radiologic, bacteriologic and other diagnostic procedures.[39-42,46]

The lesion most commonly underlying this syndrome is an islet cell adenoma or adenocarcinoma. Other conditions that may be complicated by chronic watery diarrhea include neuroblastoma, ganglioneuroma, pheochromocytoma, islet cell hyperplasia and bronchogenic carcinoma. The syndrome may be simulated by the surreptitious intake of certain drugs, such as laxatives and diuretics.

There is considerable evidence that this syndrome is mediated by a hormonal substance or substances secreted by the islet cell tumors or other causative lesions, and that the principal mediator is VIP. Evidence for this mediator role is as follows:[47]

1. The actions of VIP in experimental animals, which parallel the clinical manifestations of the syndrome, include stimulation of water and electrolyte secretion (and mucosal adenylate cyclase) from the small and large intestine; suppression of gastric acid secretion; hyperglycemia; raised serum Ca^{++}; relaxation of gallbladder and gastric smooth muscle; and vasodilation and hypotension.
2. Patients with the watery diarrhea syndrome and underlying tumors have elevated plasma levels of VIP.
3. In those patients in whom pre- and post-operative measurements are made, plasma peptide levels fall to the normal range with removal of the tumor and relief of the diarrhea.
4. Extracts of such tumors are rich in VIP immunoreactivity and VIP-like biologic activity.
5. Infusions of VIP induce watery diarrhea in dogs and also a picture resembling the clinical syndrome in pigs, at circulating levels of the peptide

similar to those observed in the human disease state.

Some skepticism has been expressed regarding the diagnostic value of plasma VIP measurement in the watery diarrhea syndrome, on the grounds that in earlier RIA's elevated VIP levels were found in some patients with watery diarrhea but without VIP-secreting tumors or islet-cell hyperplasia. Furthermore, some patients with the syndrome have been reported to have increased plasma levels of other hormonal agents that can produce or aggravate watery diarrhea; e.g., pancreatic polypeptide and prostaglandins.

Recent improvements in the VIP RIA virtually have eliminated the "false positive" results previously noted. Pancreatic polypeptide is present in high concentrations in a variety of islet cell tumors (including insulinomas, gastrinomas, glucagonomas and VIP-omas) and in plasma from these patients, but this peptide has not been found in neurogenic tumors producing watery diarrhea. Further, the biologic effects of PP in experimental animals do not include the production of secretory diarrhea. It appears, therefore, that while certain diarrheogenic islet cell tumors may secrete additional hormones that can contribute to the production of diarrhea, VIP probably is the major humoral mediator of the syndrome.[47,48]

Diarrheogenic tumors are less common than ulcerogenic tumors, but the pancreatic cholera syndrome is not altogether rare. From referrals for VIP assays to our laboratory, my colleagues and I know of at least 50 proven cases due to islet cell and other tumors that have been diagnosed within the past two to three years.

The Glucagonoma Syndrome[49,50]: A syndrome accompanying glucagon-secreting α cell tumors of the pancreas recetnly has been recognized. The syndrome

includes a necrolytic migratory erythema of the central part of the face, lower abdomen, groin, buttocks, thighs and perineum; glossitis, stomatitis and angular cheilitis; diabetes mellitus; weight loss; a normocytic, normochromic anemia; and elevated plasma glucagon levels. Skin lesions usually are the key to the diagnosis. By late 1976, 15 documented cases of the syndrome had been reported.

Familial hyperglucagonemia, without evidence of glucagonoma, has been described as an autosomal dominant disorder which is possibly related to the MEA syndrome (see above).

Somatostatinoma[51,52]: Two cases recently have been reported of islet cell tumors presenting with diabetes mellitus, hypoglucagonemia and hypoinsulinemia; one patient also showed hypochlorhydria and steatorrhea. In both cases, the diagnosis was made at cholecystectomy; inhibition of gallbladder contraction by somatostain could have led to bile stasis and cholelithiasis.

The onset of diabetes as a feature of chronic hypersomatostatinemia seems at first to be paradoxical, since the dominant effect of somatostatin given over a short period of time is the suppression of glucagon secretion and the consequent lowering of blood gluccose concentration. The clinical manifestations of somatostatinoma are also notable for their relative mildness in view of the potent and broad inhibitory activity of this peptide.

Pancreatic Polypeptide in Tumors[53]: As noted earlier, PP has been found in high concentrations in many types of pancreatic endocrine tumors, including gastrinomas, VIP-omas, glucagonomas and insulinomas. In some of these cases, plasma levels of PP also were elevated. However, no instance of a tumor secreting only PP has been reported. Blood levels of this peptide, therefore, may prove useful as a marker for islet cell tumors. More recently, this notion has been challenged.[53a]

Substance P in Carcinoid[37]: Substance P immunoreactivity recently has been found in abdominal carcinoid tumors and their metastases. The peptide is localized in the EC cell system, which also produces serotonin (5-hydroxytryptamine), the main secretory product in carcinoid tumors. The release of substance P from these tumors (for actions, see above) may contribute to the clinical syndrome, but the extent of such contribution has not been determined.

Insulinoma: The well recognized entity of insulinoma, resulting from β cell tumors of the islets, is not reviewed here, as insulin is not commonly regarded as a GI hormone.

GI HORMONES IN OTHER PATHOLOGIC STATES

GI Hormones and the Lower Esophageal Sphincter (LES)[21]: A number of GI hormones have been linked to the regulation of LES function, which is important in preventing reflux of gastric contents. The ability of exogenous gastrin to elicit contraction of the LES is undisputed, but the possibility that physiologic concentrations of gastrin are responsible for normal LES pressure is considered remote because of several reasons. First, blood levels of the hormone required to stimulate contraction of the sphincter are well above those that can be attained endogenously. Second, when antiserum to gastrin is given intravenously to oppossums -- in sufficient doses to bind more than 90% of the circulating gastrin -- it inhibits acid-secretory and sphincter responses to exogenous gastrin but does not lower basal LES pressure. Third, LES function is normal in patients with pernicious anemia and those with the Z-E syndrome, two conditions characterized by marked hypergastrinemia. Finally, no correlation has been found between fasting serum gastrin levels and LES pressure in subjects with normal or

altered sphincter function.

Motilin is another GI hormone that contracts the LES; its possible contribution to resting sphincter pressure therefore has been investigated. Again, no correlation has been found between sphincter pressure and serum motilin levels.

Among inhibitors of LES tone, VIP is particularly potent. Its inhibitory effect has been demonstrated in the opossum[54] (in which the LES is similar to that of man) and, more recently, in the baboon. In the latter, the potency of VIP in reducing LES pressure was eight times that of secretin and 32 times that of glucagon.

GI Hormones and Duodenal Ulcer Disease[55]: It is possible that gastrin is involved in subtle ways in the genesis of duodenal ulcer disease. This view is suggested by certain features of the disease: (1) an increase in parietal and peptic cell masses and, consequently, in their maximal secretion; (2) an increase in the release of gastrin after a meal (though fasting gastrin levels are normal); (3) a decrease in the suppression of gastrin by antral acidification; (4) a greater sensitivity to circulating gastrin; and (5) a greater rate of food (i.e., buffer) emptying. All of these features, it may be speculated, combine to maintain greater than normal acidification of the gastroduodenal junction.

Hepatic Failure: Some of the effects of VIP, especially the peripheral vasodilation, increased cardiac output, and stimulated respiration, recall some of the manifestations of advanced hepatic cirrhosis and failure. Further, the hypotensive and respiratory-stimulant activities of VIP are reduced markedly during passage through the liver. These observations have led to the speculation that VIP, by escaping hepatic inactivation, may

mediate some of the altered circulatory and respiratory functions in hepatic failure. This speculation is supported by reports that the circulating levels of the peptide often are elevated in patients with this disorder.

DIAGNOSTIC AND THERAPEUTIC USES[56-59]

Diagnosis: Certain effects of GI hormones have led to their use in a number of diagnostic procedures. Such uses have included:

1. Gastrin, for testing maximal stimulation of gastric secretion (usually given as pentagastrin, 6 μg per kg subcutaneously or intramuscularly, or 1 μg per kg by intravenous infusion).
2. Secretin, for testing pancreatic bicarbonate response (1-2 clinical units per kg intravenously).
3. CCK-PZ, to aid in the evaluation of gallbladder function, in the visualization of the biliary tract by cholecystography and in the roentgenologic examination of the GI (1 Ivy dog unit per kg intravenously, or the equivalent dose of the synthetic C-terminal octapeptide).
4. CCK-PZ, as a test of pancreatic exocrine function.
5. Combined stimulation with secretin and CCK-PZ as a pancreatic function test.

Therapy[57, 60]: Trials of GI hormones as therapeutic agents have included the use of secretin in the treatment of duodenal ulcer (pentagastrin-induced duodenal ulcers in cats could be prevented by simultaneous infusion of secretin); the use of CCK-PZ (or cerulein, a peptide with similar actions) in paralytic ileus; the use of CCK-PZ to produce relaxation of the sphincter of Oddi; and the use of glucagon to aid in the reduction of intussusception. The therapeutic potential of the more recently isolated peptides remains largely untested, but there are a number of interesting possibilities to be explored.

VIII CONCLUSION

Endocrinology was born with the discovery of secretin, three-quarters of a century ago. Today, after the identification of a dozen more GI hormones, the GI system (along with the brain) is one of the most interesting and rewarding targets of hormone research.

Some GI hormones are unique to the gut, while others also occur in the brain, peripheral nerves, and other tissues.

GI hormones are essential for the regulation of local secretory and motor function. Some of them also influence sugar metabolism, calcium homeostasis, lipolysis, and cardiovascular, respiratory and neuronal function.

Hypersecretion of certain GI hormones, usually the result of pancreatic islet-cell or other tumors, can produce dramatic symptoms and clinical signs. In the diagnosis of these tumors, as in the study of the physiology of GI hormones, the use of radioimmunoassay has been indispensable.

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