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THE HORMONAL REGULATION OF FOOD INTAKE, DIGESTION, AND ABSORPTION

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INTRODUCTION

All animals must take in and digest food, converting it to simpler compounds that can be absorbed. These basic processes occur even in Protozoa. In higher animals the evolution of a specialized gastrointestinal tract necessitated a parallel development of mechanisms to coordinate its functioning and to

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regulate intake to the requirements of the animal. In man, food intake involves thought, whereas the processes of digestion and absorption are automatic and, in health, to a large extent unperceived. Digestion occurs both in the lumen of the upper gastrointestinal tract and at the brush border of the duodenum and jejunum. The majority of nutrients are also absorbed from the upper small intestine. Normal digestion and absorption depend on many factors: dispersion and mixing of the food, correct amount and composition of secretions, integrity of the enterocytes, normal intestinal surface area, and appropriate speed of transit of intestinal contents.

These factors must be coordinated, and historically there was controversy as to the importance of neural versus hormonal mechanisms (9). With the recent recognition that the same peptides may act as mediators in both systems, the dichotomy has been bridged (123). However, in many cases it remains unclear which control systems, from a variety of candidate neural and humoral mechanisms, are dominant in physiology. Regulation of food intake is complex, poorly understood, and of growing concern in a world with conflicting problems of starvation and obesity-related morbidity. More is known about the processes of digestion and absorption, which are regulated by mechanisms intrinsic and extrinsic to the gastrointestinal tract (Table 1). It is clear that one group of molecules, which can conveniently be termed regulatory peptides, acts in several ways to coordinate gut function. Their discovery is summarized in the next section.

REGULATORY PEPTIDES

In 1902, Bayliss & Starling (9) demonstrated that acidification of denervated small intestine caused the prompt secretion of alkaline pancreatic juice. They postulated the existence of secretin, a blood-borne messenger or "hormone" that was released into the circulation after a physiological stimulus and acted at a distant site. Although progress was slow, by the 1940s the hormonal control

Table 1 Systems regulating digestion and absorption

Intrinsic mechanisms	—structural properties, e.g. gut smooth muscle	
	—paracrine secretion[a]	"local hormones"
	—intrinsic neuronal net	
Extrinsic mechanisms	—hormonal: general hormones with effects on gut function, e.g. thyroxine, progesterone	
	: gut hormones	
	—neuronal: adrenergic, cholinergic, and peptidergic fibers of the autonomic nervous system	

[a]Regulatory peptides are involved in the mechanisms underlined.

of the gut appeared reasonably simple. Gastrin was the agent controlling gastric acid output (53). Secretin regulated pancreatic bicarbonate (9), and pancreozymin released pancreatic enzymes (74). Cholecystokinin (CCK) controlled gall bladder function (82).

A variety of other hormones were also postulated but progress was delayed because the active substances could not be purified. One factor explaining the difficulty of isolation of the gut hormones was the inherent nature of the system; although the gut contains considerable endocrine tissue, the cells are not aggregated into glands but are widely scattered. The classical endocrine approach of examining the response to the administration of extracts was difficult to interpret because the extracts often contained several active components and discrete gland ablation was not applicable. With the development of sophisticated chemical techniques, isolation and identification of tiny amounts of peptide became possible and in 1961 secretin was isolated by Jorpes & Mutt (87). Since then, a large number of substances with a presumed regulatory role, all of which have been found to be peptides, have been isolated from the gut, characterized, and synthesized.

The development of radioimmunoassay and immunocytochemistry made it possible to measure the amounts of these peptides in tissues and plasma and to locate them (16, 17, 123, 156). It is now apparent that such regulatory peptides occur not only in endocrine cells but also in neurons throughout the central and peripheral nervous systems, including the intrinsic nerves of the gut. The neuropeptides may coexist in nerve endings with classical neurotransmitters, which gives rise to further potential sites for interaction (137). Thus, regulatory peptides may act as neurotransmitters, neuromodulators, classical hormones, or local hormones and the same peptide may function in different ways depending on the stimulus or tissue. Figure 1 shows an example of an endocrine cell and peptidergic nerve.

Because of the different ways peptides may act, it is artificial to consider regulation of gut activity by only those peptides that function as traditional hormones. This chapter addresses the broader topic of control of food intake, digestion, and absorption by regulatory peptides. The role of peptides as growth factors has been well reviewed (51, 177) and is not considered here. As shown in Table 1, hormones that affect primarily target organs other than the gut and the classical divisions of the autonomic nervous system interact with the regulatory peptides to coordinate gastrointestinal function. The neural mechanisms are mentioned where necessary to understand the role of the peptides.

The number of gut regulatory peptides identified is increasing steadily (17, 124), but some groups share common features. Regulatory peptides are phylogenetically old, precursors of mammalian forms being found extensively in invertebrates. There is evidence of gene duplication with considerable se-

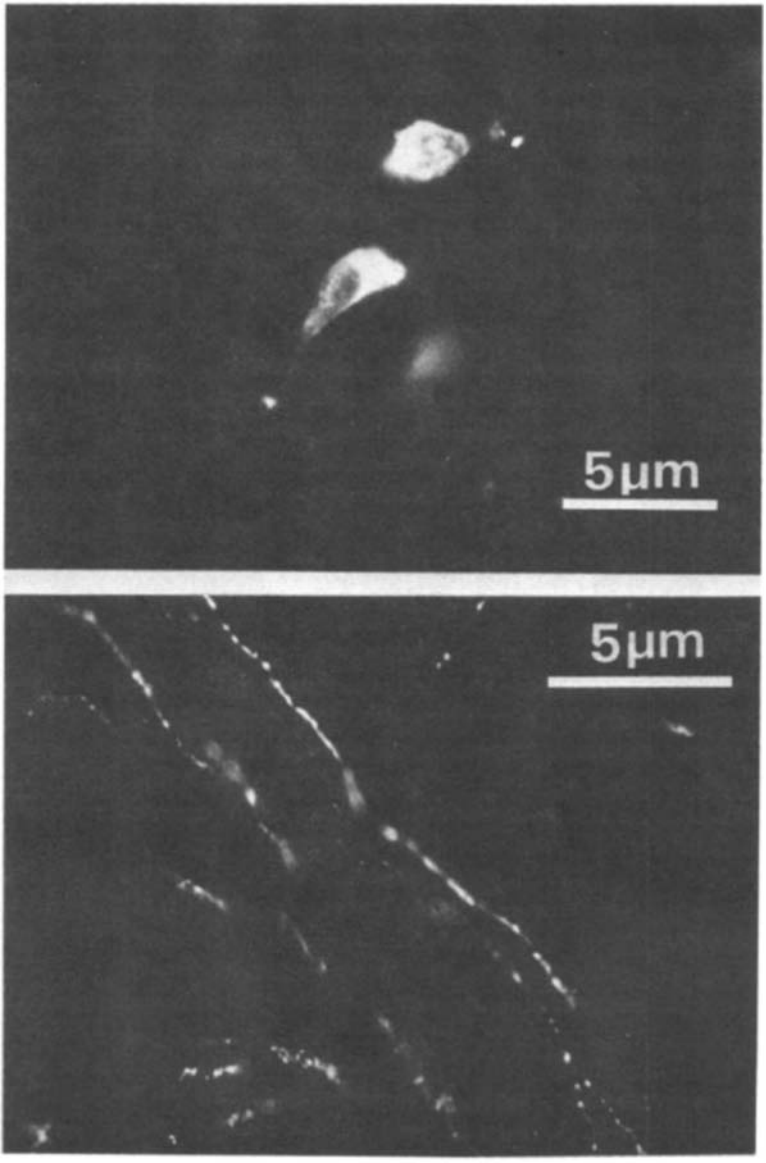

Figure 1 Photomicrographs of 10-μm cryostat sections of tissues fixed with benzoquinone solution and stained by an indirect immunofluorescent technique. *Top:* enteroglucagon cells, one showing a luminal elongation, in the mucosal epithelium of human colon. *Bottom:* circular muscle of porcine small intestine containing numerous vasoactive intestinal polypeptide–immunoreactive nerves.

quence conservation resulting in families of related peptides (8). Analysis of the physiological properties of regulatory peptides is hampered by species differences, the occurrence of multiple molecular forms with differing activities, difficulty in achieving physiological (as opposed to pharmacological) concentrations in the region of the receptors in test systems, and the enormous complexity of the interaction between control mechanisms. The major characteristics of the regulatory peptides that may be involved in the control of food intake, digestion, and absorption are listed in Table 2. These processes are considered in turn below.

FOOD INTAKE

Food intake is a complex process. The amount and type of food ingested is determined by the animal's genes, environment, and experience. Regulation has two temporal components, short-term mechanisms relating feeding to gastrointestinal activity and longer-term control maintaining nutrient stores. Different signals initiate and terminate meals, and intake is the product of meal size and frequency. Changes in intake occur in physiology and pathology.

The central and peripheral control of intake were recently reviewed (114, 142) and a scheme for possible interactions is shown in Figure 2. The complexity of the neuroanatomical and neurotransmitter bases of the central regulation of appetite is daunting. The administration of a peptide centrally or peripherally does not define its site of action (110). There has been little progress in elucidating peripheral mechanisms initiating feeding, and Cannon's gastric contraction theory is no longer tenable (143). Morley's group (116) postulated a tonic drive to eat, possibly mediated by endogenous opiates acting on the kappa receptor; appetite regulation may be achieved by inhibiting this drive. There may also be direct stimulatory mechanisms; Morley & Levine (115) recently reported that neuropeptide tyrosine (NPY) is a very potent inducer of ingestive behavior.

There is more evidence for peripheral mechanisms mediating postprandial satiety. The act of eating produces a small transient effect in esphagectomized man. Gastric distension is another postulated stimulus from common experience and food intake in dogs can be inhibited by inflating gastric balloons (120). Afferent vagal pathways were found from gastric stretch receptors, but vagotomized animals eat normally (143), so a vagal pathway does not appear to be of major physiological importance in the control of satiety. This led to a search for humoral mechanisms, and Davis et al (40) showed that if fed rats were cross-perfused to unfed rats, the unfed rats subsequently ate a smaller meal. Koopmans (91) demonstrated a gastric mediator; the instillation of food into an isolated transplanted extra stomach in rat produced satiety. Somatosta-

Table 2 Peptides in the gastrointestinal tract

Peptides in endocrine cells	Main location	Molecular forms[a]	Proposed main actions
Gastrin[b]	Antrum	17, 34	Stimulates gastric acid secretion, trophic to gastric mucosa.
Cholecystokinin[b,e]	Upper small intestine	8, 33, 39	Stimulates pancreatic enzymes, contracts gall-bladder, trophic to pancreas.
Secretin	Upper small intestine	27	Stimulates pancreatic bicarbonate secretion.
Glucose-dependent insulinotropic peptide[c]	Upper small intestine	42	Enhances insulin release.
Motilin	Upper small intestine	22	Stimulates gut motility.
Pancreatic polypeptide[d]	Pancreas	36	Inhibits pancreatic secretion, relaxes gall bladder.
Somatostatin[e]	Widespread	28, 14	Inhibits endocrine and exocrine secretion, inhibitory modulator of transmission in gut smooth muscle.
Neurotensin	Ileum	13	Inhibits gastric acid and gastric emptying, stimulates pancreatic bicarbonate.
Enteroglucagon	Ileum, colon	37, 69	Slows intestinal transit, trophic to intestinal mucosa.
Peptide tyrosine tyrosine[d]	Ileum, colon	36	Inhibits gastric acid secretion, slows intestinal transit, vasoconstriction.

Neuronal peptides	Main location	Molecular forms[a]	Proposed main actions
Gastrin-releasing peptide	Stomach and upper small intestine	27	Releases gastrin and many gut hormones.
Calcitonin gene-related peptide	Widespread	37	Inhibits gastric acid secretion, contracts gut smooth muscle.
Vasoactive intestinal peptide[c]	Widespread (especially sphincters)	28	Vasodilation; relaxes gut smooth muscle; stimulates pancreatic, biliary, and intestinal secretion; inhibits gastric acid secretion.
Peptide histidine methionine[c]	Secreted with VIP	27	Stimulates intestinal secretion.
Substance P	Widespread	11	Vasodilation, contracts gut smooth muscle, stimulates pancreatic and salivary secretion.
Enkephalins (methionine and leucine)	Widespread	5	Inhibitory modulators of transmission in gut smooth muscle.
Neuropeptide tyrosine[d]	Widespread	36	Vasoconstriction.

[a]Number of amino acid residues in the predominant molecular forms.
[b,c,d]Peptides in groups b, c, and d are closely related to other members of that group.
[c]These peptides are found in endocrine cells and nerves. Endocrine and neuronal peptides may also have paracrine functions.

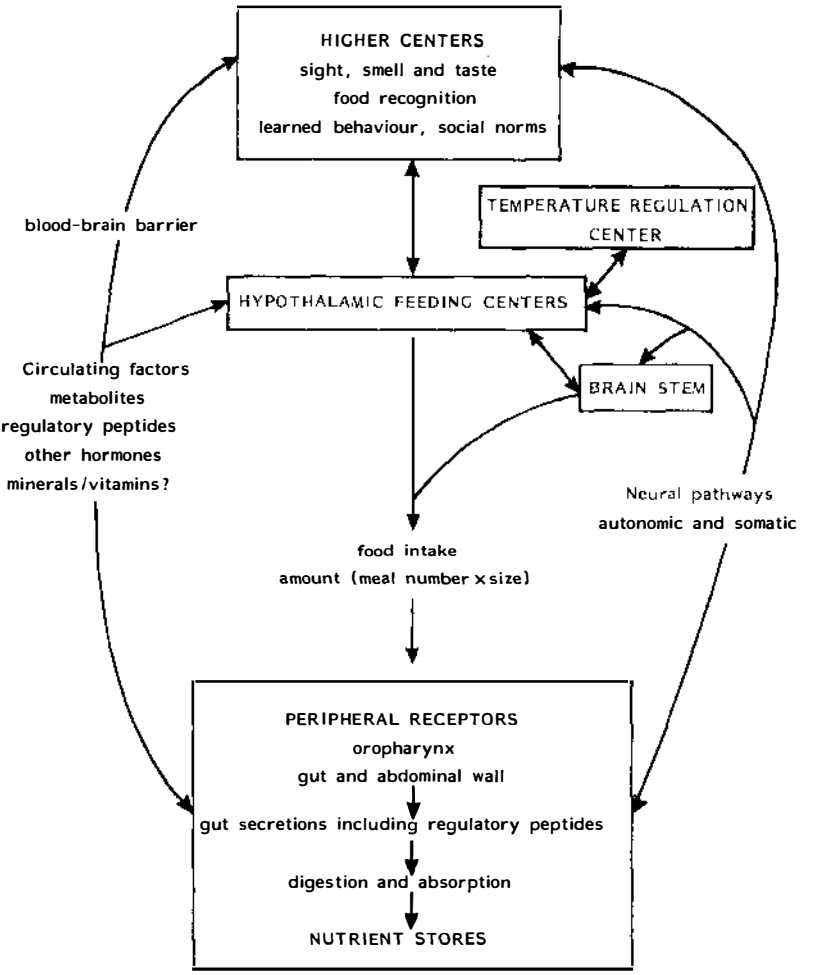

Figure 2 A scheme of the possible interactions between the central and peripheral mechanisms regulating food intake.

tin and gastrin are released by the stomach on eating but only somatostatin has satiety effects (100). Bombesin, an amphibian skin peptide (which has mammalian counterparts in the form of the two neuropeptides gastrin-releasing peptide (GRP) and neuromedin C) has a satiety effect in animals (63) that persists after vagotomy (145). However, these peptides are poor candidates as humoral satiety factors in man as there is no evidence for their release into the circulation.

Rats with open gastric fistulas feed for longer than normal, but introduction of a small amount of food into the duodenum stops feeding (97). Thus, there is

also an intestinal satiety mechanism. However, when liquid food is confined to the stomach by a cuff, rats eat normal size meals which suggests that the stomach alone can terminate a meal (46). A gastric fistula may prevent normal gastric stimulation, unmasking an intestinal effect. This could be mediated by neural reflex, a hormone, or an absorbed nutrient but the effect could be reproduced by injecting an extract of duodenal mucosa and later by purified CCK (64), or synthetic CCK.

There is now a large literature on the satiety effect of CCK. This is discussed in more detail because it illustrates the difficulty of ascribing a physiological role to a possible satiety factor. Many studies in man (88, 149) and animals (64, 144) show that exogenous CCK reduces meal size, but it has not been shown that effective doses are small enough to mimic the tiny physiological postprandial rise. The reduction in food intake is unlikely to be nonspecific due, for example, to aversive visceral sensations, because CCK elicits the entire behavioral sequence associated with satiety in animals and does not affect drinking. Other studies are contradictory, reflecting species and methodological differences, including the use of different molecular forms of CCK. In most animals CCK is effective when administered centrally or peripherally but in sheep only a central effect has been reported (43).

There is a high concentration of CCK (13, 111, 136) and its receptors (81) in the hypothalamus. Studies have looked for abnormalities of these components in animal models for obesity. CCK satiety in rats with ventromedial hypothalamic lesions (voracious eaters) is diet dependent, which suggests that CCK may affect palatability (92). In Zucker rats, CCK levels in the hypothalamus are normal (136). The observed loss of sensitivity to exogenous CCK (108, but see 175) may be associated with more subtle changes in CCK release (111) and receptor binding (60), or with peripheral effects such as delayed gastric emptying (29). Vagotomized animals were studied to define the site at which CCK exerts its satiety effects. Results are variable because of differences in techniques and associated procedures such as pyloroplasty, diet, and the health (and hence appetite) of the animal when tested postoperatively. The consensus is that vagotomy abolishes or reduces the satiety effect of CCK (142, 175), but since vagotomized animals do not overeat, this questions the importance of such a mechanism; other factors such as discomfort might be interfering. The development of a more sensitive assay for the molecular forms of CCK released on eating and studies with CCK antibodies and antagonists may contribute. In preliminary studies, CCK antibodies injected intracerebroventricularly in sheep did prolong meals (44). Proglumide in man inhibits CCK satiety (36), although it did not have any effect when administered alone.

However, despite this plethora of data, another experiment points away from a physiological role for CCK or any duodenal factor (91). In elegant parabiotic studies a 30-cm length of the small intestine of a rat pair was crossed over. Thus

food eaten by the first rat left its stomach and traversed the intestine of its pair. There was no cross-circulation. The first rat did not overeat despite the fact that CCK could not be released by its own intestine. If the second rat was fed later, it did not undereat as would be predicted. Thus, the role for any duodenal factor is unclear. A number of other peptides have also been investigated as satiety hormones (175). However, as any factor disturbing an animal may reduce food intake, and in view of the difficulty identifying a physiological effect, claims for other peptides should be interpreted with caution. It is possible that several of the peptides released when a meal is ingested may play a role in terminating that meal. The most important hormone may be gastric, but there is undoubtedly considerable interaction between humoral and neural pathways.

Short-term mechanisms must also interact with longer-term control. Rats treated chronically with CCK ate smaller but more frequent meals so that overall intake was unaltered (172). Regulation of intake in relation to energy balance is dealt with elsewhere (Woo et al, this volume) but in this context the work of Woods et al (175) is relevant. They postulate that the concentration of insulin in the cerebrospinal fluid, which is proportional to peripheral insulin over long time periods, is the signal relating fat stores to nutrient intake. Thus, the control of food intake remains the subject of intensive research. Whether this will eventually lead to the successful pharmacological manipulation of appetite in man is less certain. The sociocultural determinants of food intake may override physiological control mechanisms. As stated so eloquently by Le Mangen (96), "In humans the preparation of foods, 'la cuisine,' is an art, and eating is a chemosensory esthetic activity that largely escapes metabolic control."

DIGESTION AND ABSORPTION

Mouth

After food is ingested by man it is chewed and mixed with saliva. Salivary amylase plays a minor role in starch digestion but the lubricant function of saliva is important. The salivary glands are innervated by nerve fibers that contain vasoactive intestinal peptide (VIP), (101), substance P (75), and NPY (102). The neural control of salivary secretion is a fascinating model for other more complex systems. Parasympathetic stimulation releases acetylcholine, which causes secretion with little vasodilatation and also releases the coexisting VIP, which mediates more prolonged vasodilatation and potentiates the action of acetylcholine. Sympathetic stimulation releases norepinephrine, which also causes secretion, and also releases the co-stored NPY, which has a vasoconstrictor effect. After swallowing, a complex neurological reflex, the bolus of food passes into the esophagus.

Esophagus

The esophagus is a conduit. Its only secretion is mucus, to provide a lubricant and protective lining; its physiology was reviewed by Atkinson (6). The esophagus has a parasympathetic innervation from the dorsal vagal nuclei and a sympathetic supply from T_1 to T_6. The role of the sympathetic innervation is uncertain, as no gross disturbance in esophageal motility was seen in patients treated with bilateral thoracolumbar sympathectomy for hypertension. Incoming neurons synapse in the myenteric plexus, where silver staining reveals two types of neurons: argyrophil cells, which predominate and are believed to be interneurons; and argyrophobe cells, which supply the muscle fibers. There is evidence that acetylcholine (excitatory) and adenosine triphosphate (inhibitory) are transmitters affecting the smooth muscle (22), but a variety of putative transmitters, including the peptides substance P (95), enkephalin (163), VIP (162) and calcitonin gene-related peptide (CGRP) (128), are present in the esophageal plexus. Their role in the coordination of motility is unclear, but they may interact with acetylcholine (50).

Entry to the esophagus is controlled by the cricopharyngeus, the upper esophageal sphincter, which is under vagal control. The lower esophagus sphincter (LES) relaxes to allow entry of food to the stomach, but then remains closed forming the main barrier to gastroesophageal reflux. Control of the LES is poorly understood; intrinsic muscle tone (39), neural reflexes, and hormonal factors may all contribute. In man, truncal vagotomy impairs the normal sphincteric constriction that occurs in response to a rise in intraabdominal pressure, probably by severing the afferent limb of the reflex. Alpha-adrenergic and muscarinic agonists increase LES pressure. In some animals there are also vagal inhibitory fibers, which may be VIPergic (14, 66).

Many other peptides have been found to have pharmacological effects (6). Gastrin may act directly or via a cholinergic mechanism (178) and has been considered a strong candidate as the hormone mediating the rise in LES pressure after a meal (65), but gastrin levels in physiology (45) and pathology (105) correlate poorly with LES pressure. There may also be considerable interaction between peptides. Bombesin (37) releases gastrin from the gastric antrum and increases LES pressure, but the pressure effect cannot be entirely due to gastrin because it can be demonstrated in antrectomized animals. Somatostatin (67) decreases gastrin release but still raises the pressure. Secretin has no effect alone but competitively antagonizes the effect of gastrin (35). Thus a complex pattern of interactions emerges but it is still impossible to assign a physiological role to any of the components.

Stomach

Food passes through the LES to enter the stomach. The stomach has a parasympathetic supply from the dorsal motor nucleus of the vagus and sympathetic

innervation from T_6 to T_{10}. Several neural peptides are found in human stomach (59): VIP around the glands, substance P throughout the mucosa, and met-enkephalin and bombesin-like peptides. Gastrin (169), somatostatin (5), and motilin (30) are present in endocrine cells. The stomach receives food, liquifies it, and mixes it with its secretions. The control of gastric emptying is also important as it regulates the flow of nutrients into the small intestine and thus affects their rate of absorption.

MOTILITY AND EMPTYING Gastric motility is complex (76) and the changes initiated by eating are coordinated by several mechanisms. The proximal stomach accepts and stores food. Swallowing, and the effects of food in the stomach, induce receptive relaxation thereby inhibiting the slow contractions of the proximal stomach by a noncholinergic vagal pathway. Liquids empty rapidly but solids are only gradually released into the distal corpus and antrum, where the gastric mill breaks them down. Food is introduced into the antrum by peristalsis and vigorously retropulsed into the corpus while the pylorus remains closed. The antrum, pylorus, and proximal duodenum function as a unit allowing 1–5 ml of chyme into the duodenum about twice a minute.

Part of the first few mouthfuls of a meal rapidly enters the duodenum where the components stimulate receptors that trigger neural and hormonal pathways regulating emptying (77). Fat, carbohydrate, protein, and acid all slow emptying. Receptors are stimulated by osmotic effects (109) and the affinity for calcium (78) of the digestion products. About 200 kcal/hr pass into the duodenum, but there are no receptors for energy per se. Local and extrinsic nerve reflexes are mediated by cholinergic stimulatory, adrenergic inhibitory, and peptidergic mechanisms. Denervated pouch studies provided the major evidence for "enterogastrone" (70), a humoral mediator released by the intestine that inhibits gastric motility and secretion. Many peptides have these activities, at least in pharmacological doses (47, 171). Because of the complex functional arrangement of gastric muscle, effects on motility and emptying do not always coincide. For example, gastrin stimulates smooth muscle (112) but in the whole organ it delays emptying because antral muscle is most sensitive (79).

Secretin and CCK decrease gastric emptying but only the effect of secretin was considered physiological (165). Neurotensin, an ileal peptide released into the circulation by a mixed meal, inhibits gastric emptying (15), as does peptide tyrosine tyrosine (PPY) (4). Infusions of gastrin (151), enkephalin (139), and bombesin (133) also inhibit gastric emptying but there is doubt as to whether or not these are physiological effects. Regulatory peptides may also accelerate gastric emptying. Motilin accelerates the emptying of glucose but not fat (33), and physiological doses enhance the emptying of a solid meal in man (34). As a result of this enhanced gastric emptying, nutrients are absorbed faster. This is an example of how a peptide that exerts its primary effect on gastrointestinal

motility can have a profound secondary effect on metabolism. The effects of somatostatin are complex as low doses may enhance (99) but high doses inhibit (5) gastric emptying.

SECRETION Extensive work has been done on gastric secretion (47, 147) but the results remain controversial. The secretion of acid, bicarbonate, pepsinogen, intrinsic factor, and mucus are considered below. Mucosal blood flow, an important determinant of all aspects of gastric secretion, is reviewed elsewhere (71).

Acid Many factors interact to control acid output by the parietal cell (Figure 3). Gastric acid secretion is classically considered in cephalic, gastric, and intestinal phases but the same mechanisms are involved throughout. The sight, smell, and thought of food induce acid secretion. Secretion increases markedly when food enters the stomach although there are local negative feedback mechanisms. When food enters the duodenum there is stimulation followed by inhibition of acid secretion. Stimulation may result from the products of gastric protein digestion and inhibition from the presence of fat, acid, or hypertonic solutions. The role of central neuropeptides in the regulation of acid secretion was reviewed by Taché & Brown (152). The major peripheral acid secretogogues are histamine, gastrin, and acetylcholine. It is now accepted that these act directly on the parietal cell (1, 147).

Histamine is present in large amounts in the human stomach but control of its release from mast cells is poorly understood. It acts as a paracrine substance. In the rat, gastrin increases gastric histidine decarboxylase activity (85) and thus promotes gastric histamine production.

Gastrin (169) is discussed here in more detail because it exemplifies many of the problems in understanding the role of peptides. There are at least three molecular forms of gastrin (69) that are biologically active: big gastrin (G_{34}), little gastrin (G_{17}), and mini gastrin (G_{14}). Gastrin is mainly produced by G cells of the antrum, where G_{17} is the predominant form. Lower levels (1/10) are found in the duodenum, when G_{34} accounts for about half the total. G_{17} is more potent than G_{34} but has a shorter half-life (3 vs 15 min). In the fasting state the reported ratio of G_{34} to G_{17} is 2:1 but after meals G_{34} doubles and G_{17} quadruples so the final ratio is 1:1 (93). Detection of these molecular forms depends on the antibody used, which contributes to the confusion in the literature. The release of gastrin is controlled by the vagus, food, gastric distension, acid, and local and circulating hormones.

Early experiments showed that vagal stimulation resulted in acid secretion but a direct effect on the parietal cell could not be distinguished from gastrin-mediated release. Using a specific radioimmunoassay, Nilsson et al (119) found that sham feeding in dogs did release gastrin. A cholinergic mechanism

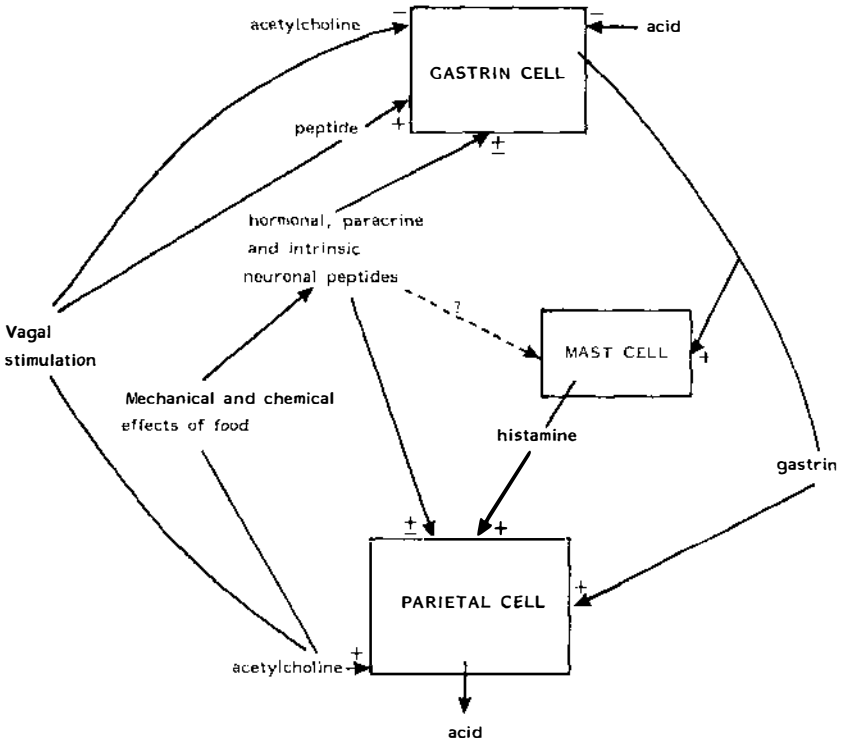

Figure 3 Possible interactions between mechanisms regulating gastric acid secretion in the human stomach.

was postulated but on reviewing the reported results it is apparent that large doses of atropine were needed and results were variable (38, 164). In man, an infusion of carbachol sufficient to cause the secretion of gastric acid did not increase gastrin (167). However, there may be species differences; in isolated rat stomachs cholinergic agonists did stimulate gastrin release (130). It has since been shown in dogs that a small dose of atropine enhances the gastrin response to food (80) and that bethanecol inhibits the bombesin-induced release of gastrin (154). Overall, it seems likely that the major vagal stimulatory pathway is noncholinergic and that the cholinergic fibers are inhibitory. There is evidence for both these vagal pathways in man. Modified sham feeding produces a small rise in gastrin (58). If the gastric pH was kept constant, a low dose of atropine increased the basal gastrin level and potentiated the gastrin response to sham feeding.

Amino acids stimulate gastrin release and in some cases directly affect the parietal cell (23). In dogs with antral pouches, the gastrin response to irrigating the pouch with Bovril is completely abolished by atropine (42). However, in

dogs with Pavlov pouches, atropine abolished the acid response to a protein meal but did not suppress the rise in gastrin (38). Thus, in normal animals food may be causing release of gastrin indirectly by a noncholinergic mechanism. In other studies with dog antral pouches, distension increased gastrin release and had a direct reflex effect on acid secretion (41). Both these mechanisms were abolished by the large dose of atropine used. Distension studies in humans using intragastric titration to maintain pH show that acid is secreted without a detectable rise in gastrin (146). Thus distension does not appear to be an important stimulus of gastrin secretion in man.

Direct feedback inhibition of acid on stimulated gastrin release from the G cells appears to be a major physiological mechanism, although the fasting serum gastrin in man is little affected by acidification of the antrum for short periods (28). If luminal pH is maintained at 2.5 the gastrin response to an amino acid meal is reduced by 80% (170). Loss of this inhibition by acid is probably the major factor causing the basal hypergastrinemia following vagotomy. Calcium and epinephrine can also stimulate gastrin release, as seen in hyperparathyroidism and pheochromocytoma, but they are unlikely to have a physiological role.

Many regulatory peptides affect gastrin release. GRP increases gastrin as its name implies (106). Secretin (157), VIP, glucose-dependent insulinotropic peptide (GIP) (127), glucagon (11), somatostatin (126), calcitonin (10), and substance P (141) all decrease gastrin release. It is not known which of these effects are physiological, but a physiological role seems unlikely for secretin, GIP, glucagon, and calcitonin. Somatostatin, which is found in large amounts in the fundus, is also present in the antrum. It is released on vagal stimulation but not by cholinergic agonists (5), and it inhibits basal and stimulated gastrin release (126). It may have a role in the regulation of both gastrin and gastric acid secretion, being secreted at low pH whereas gastrin is secreted at high pH. Glucagon, secretin, bombesin-like peptides, GIP, and VIP may act directly, or indirectly via somatostatin (31, 32, 107). Substance P and met-enkephalin decrease somatostatin release (32).

In animals vagal stimulation has a direct secretory effect on the parietal cell via a muscarinic receptor (147). In antrectomized duodenal ulcer patients sham feeding produced acid secretion without a measurable rise in gastrin (89). The nature of this pathway in man has been questioned (47) because it was reported that cholinergic agonists do not stimulate acid secretion. In the studies referred to (129), infusion of urecholine and carbacholine did not significantly increase acid but gastrin was not measured. A negative effect of the agonists or acid on the G cell could have reduced concurrent gastrin-mediated acid secretion. Cholinergic agonists did not increase the maximum pentagastrin-stimulated acid output, but the effects of low-dosage pentagastrin and urecholine were additive. Other studies demonstrated cholinergic stimulation of acid produc-

tion in man (167). It is possible that direct vagal stimulation of the parietal cell is mediated by another transmitter, but in view of this reappraisal it is not strictly necessary to invoke a noncholinergic mechanism.

Vagal inhibition of acid secretion has also been reported in dogs. Sham feeding inhibits pentagastrin-stimulated acid secretion from a Heidenhain pouch (already denervated) only if the vagus is intact (125). Cutting the extragastric vagi increases pentagastrin-stimulated acid production in a Heidenhain pouch (94). This suggests that there is an extragastric humoral mediator inhibiting acid production, "vagogastrone" (70). Many peptides inhibit acid secretion—somatostatin, secretin, VIP, GIP, glucagon, calcitonin and substance P (which also inhibit gastrin release), neurotensin (15), CGRP (121), and PYY (3). The effect of opiates is variable (90). It remains unclear which peptides have a physiological role and whether they act directly on the parietal cell or via gastrin. Infusion of CCK or secretin alone, even in pharmacological doses, cannot reproduce the magnitude of the inhibition of acid secretion in a Heidenhain pouch produced by the presence of fat in the duodenum (84), so that the "enterogastrone" effect can certainly not be produced by either CCK or secretin alone. Thus, several of the peptides released when food enters the duodenum probably act in consort with neural reflexes as the "duodenal brake," decreasing acid production and, as described in the previous section, regulating gastric emptying.

Bicarbonate Alkaline mucus is thought to play a role in protecting the gastric mucosa, and is secreted independently of gastric acid (47, 62). Calcium, CCK, and carbachol are reported to stimulate this bicarbonate production. Epinephrine, parathormone, sodium taurocholate, and ethanol decrease bicarbonate secretion. The importance of the various factors is unknown.

Pepsinogens There is a continual basal secretion of pepsinogen that can be increased by histamine, gastrin, calcium, vagal stimulation, and cholinergic agents (47, 167). Secretin inhibits acid secretion but stimulates pepsinogen secretion. Motilin has no effect on acid but weakly stimulates pepsinogen. GIP, neurotensin (15), and somatostatin inhibit pepsinogen secretion.

Intrinsic factor Vagal stimulation, acetylcholine, gastrin, and histamine all stimulate secretion of intrinsic factor (47).

Mucus Little is known about the control of mucus secretion. Local irritation seems to play a major role, but cholinergic agents and gastrin may all stimulate mucus production (47).

Small Intestine

In the small intestine, chyme is mixed with intestinal secretions, pancreatic secretions, and bile. Digestion and absorption take place as the contents are propelled distally. The actual processes of absorption of nutrients (as distinct from water and ions) are not directly regulated by neural or humoral factors. However, normal absorption can only occur if food intake, digestion (secretion and motility), and the passage of digestive products through the small intestine (gastric emptying and transit time) are properly regulated. The small intestine contains a broad array of peptides in nerves and endocrine cells. As already discussed, stimulation of receptors in the duodenum and small intestine results in neural, hormonal, and paracrine responses that integrate the function of the stomach, pancreas, biliary tree, and intestine. CCK, secretin, GIP, and motilin are the major peptides released into the circulation from the upper small intestine after a meal.

MOTILITY Motility of the fed and fasting small intestine differs markedly. Feeding interrupts the "housekeeping" migratory motor complex (174), producing a complex irregular pattern that has been the subject of extensive computer analysis (54). This pattern needs to subserve simultaneous mixing, propulsion, and absorption of the contents. In autotransplanted jejunoileal loops there is incomplete suppression of the interdigestive pattern on feeding, which suggests that both vagal and hormonal components are necessary (132). Gastrin (55, 155), insulin (20), CCK (118), secretin (117), and neurotensin (159) have all been implicated, but in no case has it been shown that the amount and molecular forms of a hormone released by a meal are effective. The role that motilin plays in regulating normal postprandial motility is unknown. It has been suggested that peptides released from the lower small intestine in the presence of digested food (peptides such as PYY, enteroglucagon, and neurotensin) may act hormonally, as an "ileal brake," regulating gastric or jejunal motility. There is evidence in malabsorption conditions for such a mechanism (148). Fat infused into the normal ileum inhibits jejunal motility. This is accompanied by a rise in enteroglucagon but the time course of the rise does not parallel the changes in motility, so other factors may be involved.

SECRETION Mucus is secreted by the duodenal Brunner's glands and goblet cells. Intestinal juice is secreted from the crypts of Lieberkuhn (62). Intestinal secretion itself contains no enzymes but the brush border of the epithelial cells contains peptidases, disaccharidases, and lipase. Extrinsic and intrinsic nerves and paracrine and endocrine mechanisms all influence intestinal secretion. CCK, glucagon, and GIP induce secretion in man (161), but they are not

effective at their probable physiological concentrations. Interactions may be necessary; for example gastrin, secretin, GIP, and glucagon infused together in physiological doses did cause secretion (122). There is better evidence for vagal muscarinic stimulation of secretion and alpha-adrenergic stimulation of absorption (27). Among the neural peptides, VIP, peptide histidine isoleucine (PHI) (113), substance P, and bombesin can all induce secretion in vivo and somatostatin and enkephalins are inhibitory (161).

Pancreas

The exocrine pancreas secretes enzymes from acinar cells and bicarbonate from ductule epithelium. Pancreatic juice has two components: a chloride-rich secretion and enzymes from the acinar cells, and a bicarbonate-rich secretion from the ductules (26). The latter constitutes most of the volume of pancreatic secretion in man. As with the stomach, feeding interrupts an interdigestive secretory pattern and increases pancreatic secretion (48). There is an initial cephalic phase (131). In man this is probably due to vagal stimulation of the pancreatic acini, as an enzyme response can be obtained postgastrectomy (when neither gastrin nor acid stimulation of the duodenum could be responsible) (138). Thereafter, the pancreatic response depends on the composition of the meal. Gastric distension (173) and chemical stimulation (138) increase enzyme secretion probably by neural reflexes and gastrin. When acid chyme enters the duodenum there is a brisk secretion of pancreatic water and bicarbonate in addition to enhanced enzyme output. The increased secretion of water and bicarbonate has been attributed to secretin, and that of enzymes to CCK [when CCK was isolated it was found to have the activity of pancreozymin (74)].

Secretin has an extremely potent effect on bicarbonate secretion. However, it has only recently been possible to demonstrate that it is released after a meal as it is secreted in small amounts in transient spikes, which reflects the gastric emptying of an acid chyme (134). Infusion of a dose of secretin that mimics postprandial levels is associated with bicarbonate secretion, but the amount of bicarbonate produced is less than that after a meal (135). Infusions of CCK (176) and vagal stimulation (19) potentiate the effect of secretin. The effect of vagal stimulation is atropine-resistant, which may mean that a peptide transmitter is involved. VIP can be released by neural stimulation of the pancreas in cat and also causes pancreatic secretion (57). CCK levels rise after a meal (2). Thus, in intact man pancreatic bicarbonate secretion may well be mediated by an interaction between these mechanisms.

The pancreatic acinar cell has receptors for five families of secretagogues (61). Receptors for muscarinic agonists, CCK/gastrin, GRP, and substance P are linked to an intracellular mechanism regulating calcium release and increasing cyclic guanosine monophosphate. The secretin/VIP receptor activates

adenyl cyclase. Peptides may interact directly (21) or indirectly, for example by altering blood flow. Thus, there is potential for many factors to stimulate pancreatic enzyme secretion. Pavlov had originally postulated a neural component to the intestinal phase of pancreatic enzyme secretion, but until recently this had been overlooked and it was accepted that this response was mediated by hormonal CCK. The CCK response to food was difficult to assess because most CCK antibodies cross-react with gastrin. However, use of specific *N*-terminal antibodies demonstrated that there is a postprandial rise in CCK (2, 24). Infusions of CCK_{33} that mimic these levels, on a background of secretin, do stimulate pancreatic enzyme secretion in man (166). However, studies of the time lapse between stimulus and response suggest that enzyme secretion cannot be entirely hormonally mediated (140). The latency of the pancreatic responses to intraduodenal oleate and tryptophan were significantly shorter than the latency of the response to the intraportal injection of CCK given as a bolus on a background of secretin. Atropine and truncal vagotomy increased the latency to intraduodenal stimulation; hence a vagovagal cholinergic reflex may mediate the early enzyme response to intestinal stimulants. The contributions of neural and hormonal mechanisms remain to be determined.

Inhibitors of pancreatic secretion, including pancreatic polypeptide (12, 68) and somatostatin (72), have also been described. Excitation of the splanchnic nerve causes vasoconstriction and inhibition of secretion (7). Infusion of nonphysiological solutions into the terminal ileum of anesthetized cat was also found to inhibit pancreatic secretion and this "pancreatone" effect persisted in denervation studies (73). The nature of the hormone(s) involved is unknown, but one candidate is PYY, a peptide found in high concentration in endocrine cells of the distal intestine in animals, including man (124). It inhibits stimulated pancreatic secretion in the cat (153). However, the contribution of such mechanisms to physiological control remains unknown.

Biliary Tract

Hepatocytes secrete bile acids, water, and electrolytes into the canaliculi by bile acid–dependent and bile acid–independent mechanisms (18, 158). Water and bicarbonate are added in the ductules. Bile is stored and concentrated in the gall bladder, which contracts about twice during a meal and periodically in the interdigestive phase so that bile passes toward the duodenum. Bile flow into the duodenum is regulated by the intraduodenal segment of the common bile duct and the sphincter of Oddi. The biliary tree has a parasympathetic and sympathetic supply and contains several peptides. In the guinea pig, VIP, substance P, met-enkephalin, somatostatin, and bombesin-like peptides have been identified in nerves; somatostatin is present also in endocrine cells (25).

Several factors can stimulate bile flow: insulin and glucagon at the canaliculus, and secretin, VIP, CCK, gastrin, and vagal stimulation probably at the

ductule level (86, 158, 160). Substance P and somatostatin inhibit bile flow (103). CCK (82) and bombesin contract the gall bladder; the effect of bombesin is probably secondary to CCK release (56). Secretin may potentiate the effect of CCK (150). Several peptides relax the gall bladder and CCK, secretin, and gastrin relax the sphincter of Oddi (98). Vagotomy results in a tendency for the gall bladder to dilate at rest, but it still empties normally in response to a meal or CCK. It is difficult to determine which of this multiplicity of pharmacological effects are important.

The major determinant of bile flow is bile acid secretion and therefore there must be an intact enterohepatic circulation. For years it was accepted that gall bladder contraction was mediated by CCK released by the products of fat and protein digestion in the small intestine. However, many aspects of this system are poorly understood (49). It is necessary to demonstrate that the amount and forms of CCK released in response to a meal compare with those found on infusion to stimulate the gall bladder, and that the time course of the response is compatible with a hormonal mechanism. This is still under review, although a hormonal mechanism is once more attracting support (104).

Colon

The major functions of the colon are the reabsorption of water and electrolytes and storage of feces. However, the colon, too, has a significant number of endocrine cells (15a, 124). Colonic hormones may help to integrate upper and lower gut functions. Infusions of nonphysiological substances into the colon of cat and man demonstrated inhibitory effects on gastric, pancreatic, and biliary secretion (73, 83a) but the significance of these effects is unknown.

CONCLUSION

The regulation of food intake, digestion, and absorption has occupied physiologists for over 100 years and continues to do so. Early ideas that neural mechanisms were dominant were discarded as a simple system of gut hormones was discovered. However, in the last ten years radioimmunoassay and immunocytochemistry have demonstrated that the gut is an extremely complex organ containing a large number of regulatory peptides in nerves and endocrine cells. These peptides have neurocrine, endocrine, and paracrine functions. Studies with synthetic peptides are removing some of the confusion caused by earlier studies with active extracts. Closer analysis of several accepted hormonal mechanisms has thrown doubt on their physiological validity. However, the use of nonphysiological doses and inappropriate molecular forms of peptides generated its own share of uninterpretable phenomenology. All aspects of the regulation of food intake, digestion, and absorption are controlled by a complex interaction between neurohumoral mechanisms in the brain and periphery.

Recent studies at a cellular level are providing clear documentation of receptors and secretory responses, allowing us to understand the potential for interaction between classical and peptide neurotransmitters, hormones and paracrine substances. It will then be possible to determine which factors from the spectrum of candidate neural and humoral mechanisms are dominant in physiology. This will lead to a more rational therapeutic approach when pathology intervenes.

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Literature Cited

1. Ackerman, S. H. 1982. Ontogeny of gastric acid secretion in the rat: evidence for multiple response systems. *Science* 217:75–77
2. Adrian, T. E., Bacarese-Hamilton, A. J., Bloom, S. R. 1983. Measurement of cholecystokinin octapeptide using a new specific radioimmunoassay. *Regul. Peptides* 7:271 (Abstr.)
3. Adrian, T. E., Savage, A. P., Sagor, G. R., Bacarese-Hamilton, A. J., Polak, J. M., et al. 1984. PYY infusion in man: metabolism and secretory effects. *Dig. Dis. Sci.* 29:3S (Abstr.)
4. Allen, J. M., Adrian, T. E., Fitzpatrick, M. L., Yeates, J. C., Bloom, S. R. 1984. Gastric emptying in man: response to peptide YY and neuropeptide Y. *Dig. Dis. Sci.* 29:4S (Abstr.)
5. Arnold, R., Lankisch, P. G. 1980. Somatostatin and the gastrointestinal tract. *Clin. Gastroenterol.* 9:733–53
6. Atkinson, M. 1983. The physiology of the oesophagus. See Ref. 83, pp. 35–48
7. Barlow, T. E., Greenwell, J. R., Harper, A. A., Scratcherd, T. 1974. The influence of the splanchnic nerves on the external secretion, blood flow and electrical conductance of the cat pancreas. *J. Physiol. London* 236:421–33
8. Barrington, E. J. W. 1982. Evolutionary and comparative aspects of gut and brain peptides. *Br. Med. Bull.* 38:227–32
9. Bayliss, W. M., Starling, E. H. 1902. The mechanism of pancreatic secretion. *J. Physiol. London* 28:325–53
10. Becker, H. D., Reeder, D. D., Scurry, M. T. 1974. Inhibition of gastrin release and gastric secretion by calcitonin in patients with peptic ulcer. *Am. J. Surg.* 127:71–75
11. Becker, H. D., Reeder, D. D., Thompson, J. C. 1975. Effect of glucagon on circulating gastrin. *Gastroenterology* 65: 28–35
12. Beglinger, C., Taylor, I. L., Grossman, M. I., Solomon, T. E. 1984. Pancreatic polypeptide inhibits exocrine pancreatic responses to six stimulants. *Am. J. Physiol.* 246:G286–91
13. Beinfield, M. C., Meyer, D. K., Eskay, R. L., Jensen, R. T., Brownstein, M. J. 1981. The distribution of cholecystokinin immunoreactivity in the central nervous system of the rat as demonstrated by radioimmunoassay. *Brain Res.* 212:151–57
14. Biancani, P., Walsh, J. H., Behar, J. 1984. Vasoactive intestinal polypeptide: A neurotransmitter for lower esophageal sphincter relaxation. *J. Clin. Invest.* 73:963–67
15. Blackburn, A. M., Fletcher, D. R., Bloom, S. R., Christofides, N. D., Long, R. G., et al. 1980. Effect of neurotensin on gastric function in man. *Lancet* 1:987–89

15a. Bloom, S. R. 1981. Normal and disordered function of the colon: regulatory peptides. In *Colorectal Disease,* ed. J. P. S. Thomson, R. J. Nicholls, C. B. Williams, p. 55. London: William Heinemann Medical Books

16. Bloom, S. R., Long, R. G., eds. 1982. *Radioimmunoassay of Gut Regulatory Peptides*. London: Saunders
17. Bloom, S. R., Polak, J. M., eds. 1981. *Gut Hormones*. Edinburgh: Churchill Livingstone
18. Boyer, J. L., Bloomer, J. R. 1974. Canalicular bile secretion in man. *J. Clin. Invest.* 54:773–81
19. Brown, J. C., Harper, A. A., Scratcherd, T. 1967. Potentiation of secretin stimulation of the pancreas. *J. Physiol. London* 190:519–30

20. Bueno, L., Rukebusch, M. 1976. Insulin and jejunal electrical activity in dogs and sheep. *Am. J. Physiol.* 230:1538–44
21. Burnham, D. B., McChesney, D. J., Thurston, K. C., Williams, J. A. 1984. Interaction of cholecystokin and vasoactive intestinal polypeptide on function of mouse pancreatic acini in vitro. *J. Physiol. London* 349:475–82
22. Burnstock, G., Campbell, G., Satchell, D., Symthe, A. 1970. Evidence that adenosine triphosphate or a related nucleotide is the transmitter substance released by non-adrenergic inhibitory nerves in the gut. *Br. J. Pharmacol.* 40:668–88
23. Byrne, W. J., Christie, D. L., Ament, M. E., Walsh, J. H. 1977. Acid secretory response in man to 18 individual amino acids. *Clin. Res.* 25:108 (Abstr.)
24. Byrnes, D. J., Henderson, L., Borody, T., Rehfeld, J. F. 1981. Radioimmunoassay of cholecystokinin in human plasma. *Clin. Chim. Acta* 111:81–89
25. Cai, W., Gu, J., Huang, W., McGregor, G. P., Ghatei, M. A., et al. 1983. Peptide immunoreactive nerves and cells of the guinea-pig gall bladder and biliary pathways. *Gut* 24:1186–93
26. Case, R. M., Hunter, M., Novak, I., Young, J. A. 1983. A comparison of the mechanisms of electrolyte secretion in pancreas and salivary glands. *Scand. J. Gastroenterol.* 18(Suppl. 87):57–67
27. Chang, E. B., Field, M., Miller, R. J. 1982. Alpha-adrenergic receptor regulation of ion transport in rabbit ileum. *Am. J. Physiol.* 242:G237–42
28. Chayvialle, J. A., Lambert, R., Touillon, C., Moussa, F. 1977. Antral acidification and gastrin release in man. See Ref. 156, pp. 447–59
29. Chey, W. Y., Hitanant, S., Hendricks, J., Lorber, S. H. 1970. Effect of secretin and cholecystokinin on gastric emptying and gastric secretion in man. *Gastroenterology* 58:820–27
30. Chey, W. Y., Lee, K. Y. 1980. Motilin. *Clin. Gastroenterol.* 9:645–56
31. Chiba, T., Taminato, T., Kadowaki, S., Abe, H., Chihara, K., et al. 1980. Effects of glucagon, secretin and vasoactive intestinal polypeptide on gastric somatostatin and gastrin release from the isolated perfused rat stomach. *Gastroenterology* 79:67–71
32. Chiba, T., Taminato, T., Kadowaki, S., Inoue, Y., Mori, K., et al. 1980. Effects of various gastrointestinal peptides on gastric somatostatin release. *Endocrinology* 106:145–49
33. Christofides, N. D., Long, R. G., Fitzpatrick, M. L., McGregor, G. P., Bloom, S. R. 1980. Effect of motilin on the gastric emptying of glucose and fat in man. *Gastroenterology* 80:456–60
34. Christofides, N. D., Modlin, I. M., Fitzpatrick, M. L., Bloom, S. R. 1979. Effect of motilin on the rate of gastric emptying and gut hormone release during breakfast. *Gastroenterology* 76:903–7
35. Cohen, S., Lipshutz, W. 1971. Hormonal regulation of human lower esophageal sphincter competence. Interaction of gastrin and secretin. *J. Clin. Invest.* 50:449–54
36. Collins, S., Walker, D., Forsyth, P., Belbeck, L. 1983. The effects of proglumide on cholecystokinin, bombesin and glucagon induced satiety in the rat. *Life Sci.* 32:2223–29
37. Corazziari, E., Delle Fave, G., Pozzessere, C., Kohn, A., De Magistris, L., et al. 1982. Effect of bombesin on lower esophageal sphincter pressure in humans. *Gastroenterology* 83:10–14
38. Csendes, A., Walsh, J. H., Grossman, M. I. 1972. Effects of atropine and antral acidification on gastrin release and acid secretion in response to insulin and feeding in dogs. *Gastroenterology* 63:257–63
39. Daniel, E. E., Taylor, G. S., Holiman, M. E. 1976. The myogenic basis of active tension in the lower esophageal sphincter. *Gastroenterology* 70:874 (Abstr.)
40. Davis, J. D., Gallagher, R. J., Ladove, R. F., Turansky, A. J. 1969. Inhibition of food intake by a humoral factor. *J. Comp. Physiol. Psychol.* 67:407–17
41. Debas, H. T., Konturek, S. J., Walsh, J. H., Grossman, M. I. 1974. Proof of a pyloro-oxyntic reflex for stimulation of acid secretion. *Gastroenterology* 66: 526–32
42. Debas, H. T., Walsh, J. H., Grossman, M. I. 1977. Mechanisms of release of antral gastrin. See Ref. 156, pp. 425–35
43. Della-Fera, M. A., Baile, C. A. 1980. Cerebral ventricular injections of CCK—octapeptide and feed intake: the importance of continuous injection. *Physiol. Behav.* 24:1133–38
44. Della-Fera, M. A., Baile, C. A., Schneider, B. S., Grinker, J. A. 1981. Cholecystokinin antibody injected in cerebral ventricles stimulates feeding in sheep. *Science* 212:687–89
45. Dent, J., Hansky, J. 1976. Relationship of the serum gastrin response to lower esophageal sphincter pressure. *Gut* 17:144–46
46. Deutsch, J. A., Young, W. G., Kalogeris, T. J. 1978. The stomach signals satiety. *Science* 201:165–67

47. Dick, J. A. 1983. The control of gastric secretion. *Br. J. Hosp. Med.* 30:28–33
48. Di Magno, E. P. 1983. Alterations and consequences of interdigestive and post-stimulatory human exocrine pancreatic secretion in health and disease. *Scand. J. Gastroenterol.* 18(Suppl. 87):69–84
49. Dockray, G. J. 1982. The physiology of cholecystokinin in brain and gut. *Br. Med. Bull.* 38:253–58
50. Domoto, T., Jury, J., Berezin, I., Fox, J. E. T., Daniel, E. E. 1983. Does substance P co-mediate with acetylcholine in nerves of opossum esophageal muscularis mucosa? *Am. J. Physiol.* 245:G19–28
51. Dowling, R. H. 1982. Intestinal adaptation and its mechanisms. See Ref. 83, pp. 135–56
52. Deleted in proof
53. Edkins, J. S. 1905. On the chemical mechanism of gastric secretion. *Proc. R. Soc. London Ser. B* 76:376
54. Eeckhout, C., Vantrappen, G., Hellemans, J., Janssens, J., De Wever, I. 1982. Patterns of digestive myoelectrical activity. *In Motility of the Digestive Tract*, ed. M. Wienbeck, pp. 433–36. New York: Raven
55. Erckenbrecht, J. F., Caspan, J., Wienbeck, M. 1984. Pentagastrin induced motility in the human upper gastrointestinal tract is reversed by proglumide. *Gut* 25:953–56
56. Erspamer, V., Improta, G., Melchiorri, P., Sopranzi, N. 1974. Evidence of cholecystokinin release by bombesin in the dog. *Br. J. Pharmacol.* 52:227–32
57. Fahrenkrug, J., Schaffalitzky de Muckadell, O. B., Holst, J. J., Lindkaer-Jensen, S. 1979. Vagal vipergic control of pancreatic fluid and bicarbonate secretion. In *Gastrins and the Vagus*, ed. J. F. Rehfeld, E. Amdrup, pp. 123–32. London: Academic
58. Feldman, M., Richardson, C. T. D., Taylor, I. L., Walsh, J. H. 1979. Effect of atropine on vagal release of gastrin and pancreatic polypeptide. *J. Clin. Invest.* 63:294–98
59. Ferri, G.-L., Botti, P., Biliotti, G., Rebecchi, L., Bloom, S. R., et al. 1984. VIP, substance P and met-enkephalin immunoreactive innervation of the human gastroduodenal mucosa and Brunner's glands. *Gut* 25:948–52
60. Finkelstein, J. A., Steggles, A. W., Martinez, P. A., Praisman, M. 1984. Cholecystokinin receptor binding levels in the genetically obese rat brain. *Peptides* 5:11–14
61. Gardner, J. D., Jensen, R. T. 1983. Gastrointestinal peptides: The basis of action at a cellular level. *Rec. Prog. Horm. Res.* 39:211–43
62. Garner, A., Flemstrom, G. 1981. Local alkaline secretion. See Ref. 17, pp. 186–91
63. Gibbs, J., Fauser, D. J., Rowe, E. A., Rolls, B. J., Rolls, E. T., et al. 1979. Bombesin suppresses feeding in rats. *Nature* 282:208–10
64. Gibbs, J., Young, R. C., Smith, G. P. 1973. Cholecystokinin decreases food intake in rats. *J. Comp. Physiol. Psychol.* 84:488–95
65. Giles, G. R., Mason, M. C., Humphries, C., Clark, C. G. 1969. Action of gastrin on the lower esophageal sphincter in man. *Gut* 10:730–34
66. Goyal, R. K., Rattan, S. 1980. VIP as a possible neurotransmitter of non-cholinergic non-adrenergic inhibitory neurones. *Nature* 288:378–80
67. Greco, A. V., Bianco, A., Altomonte, L., D'Acquarica, L., Ghirlanda, G. 1982. Effect of somatostatin on lower esophageal sphincter pressure and serum gastrin in normal and achalasic subjects. *Horm. Metab. Res.* 14:26–28
68. Greenberg, G. R., McCloy, R. F., Adrian, T. E., Chadwick, V. S., Baron, J. H., et al. 1978. Inhibition of pancreas and gallbladder by pancreatic polypeptide. *Lancet* 2:1280–82
69. Gregory, R. A. 1982. Heterogeneity of gut and brain regulatory peptides. *Br. Med. Bull.* 38:271–76
70. Grossman, M. I. 1974. Candidate hormones of the gut. *Gastroenterology* 67:730–55
71. Guth, P. H. 1982. Stomach blood flow and acid secretion. *Ann. Rev. Physiol.* 44:3–12
72. Hanssen, L. E., Hanssen, K. F., Myren, J. 1977. Inhibition of secretin release and pancreatic bicarbonate secretion by somatostatin infusion in man. *Scand. J. Gastroenterol.* 12:391–94
73. Harper, A. A., Hood, A. J. C., Mushens, J., Smy, J. R. 1979. Inhibition of external pancreatic secretion by intracolonic and intraileal infusions in the cat. *J. Physiol. London* 292:445–54
74. Harper, A. A., Raper, H. S. 1943. Pancreozymin, a stimulant of the secretion of pancreatic enzymes in extracts of the small intestine. *J. Physiol. London* 102:115–25
75. Hokfelt, T., Johansson, O., Kellerth, J. O., Ljungdahl, A., Nilsson, G., et al. 1977. Immunohistochemical distribution of substance P. In *Substance P*, ed. U. S. von Euler, B. Pernow, pp. 117–45. New York: Raven
76. Hunt, J. N. 1983. Mechanisms and dis-

orders of gastric emptying. *Ann. Rev. Med.* 34:219–29
77. Hunt, J. N., Knox, M. T. 1968. Regulation of gastric emptying. In *Handbook of Physiology, Sect. 6: Alimentary Canal*, ed. C. F. Code, 4:1917–35. Washington, DC: Am. Physiol. Soc.
78. Hunt, J. N., McHugh, P. R. 1982. Does calcium mediate the slowing of gastric emptying in primates? *Am. J. Physiol.* 243:G200–3
79. Hunt, J. N., Ramsbottom, N. 1967. Effect of gastrin II on gastric emptying and secretion during a test meal. *Br. Med. J.* 4:386–87
80. Impicciatore, M., Walsh, J. H., Grossman, M. I. 1977. Low doses of atropine enhance serum gastrin response to food in dogs. *Gastroenterology* 72:995–96
81. Innis, R. B., Snyder, S. H. 1980. Distinct cholecystokinin receptors in brain and pancreas. *Proc. Natl. Acad. Sci. USA* 77:6917–21
82. Ivy, A. C., Oldberg, E. 1928. A hormone mechanism for gallbladder contraction and evacuation. *Am. J. Physiol.* 86:599–613
83. Jewell, D. P., Selby, W. S., eds. 1982. *Topics in Gastroenterology, 10*. Oxford: Blackwell Scientific
83a. Jian, R., Besterman, H. S., Sarson, D. L., Aymes, C., Hostein, J., et al. 1981. Colonic inhibition of gastric secretion in man. *Dig. Dis. Sci.* 26:195–201
84. Johnson, L. R., Grossman, M. I. 1969. Effect of fat, secretin and cholecystokinin on histamine stimulated gastric secretion. *Am. J. Physiol.* 216:1176–79
85. Johnson, L. R., Jones, R. S., Aures, D., Hakanson, R. 1969. Effect of antrectomy on gastric histidine decarboxylase activity in the rat. *Am. J. Physiol.* 216:1051–53
86. Jones, R. S., Grossman, M. I. 1970. Choleretic effects of cholecystokinin, gastrin II and cerulein in the dog. *Am. J. Physiol.* 219:1014–18
87. Jorpes, J. E., Mutt, V. 1961. On the biological activity and amino acid composition of secretin. *Acta Chem. Scand.* 15:1790–91
88. Kissileff, H. R., Pi-Sunyer, F. X., Thornton, J., Smith, G. P. 1981. C-terminal octapeptide of cholecystokinin decreases food intake in man. *Am. J. Clin. Nutr.* 34:154–60
89. Knutson, U., Olbe, L., Ganguli, P. C. 1974. Gastric acid and plasma gastrin responses to sham feeding in duodenal ulcer patients before and after resection of the antrum and duodenal bulb. *Scand. J. Gastroenterol.* 9:351–56
90. Konturek, S. J. 1981. Action of the enkephalins on the digestive system. See Ref. 17, pp. 432–40
91. Koopmans, H. S. 1981. The role of the gastrointestinal tract in the satiation of hunger. In *The Body Weight Regulatory System: Normal and Disturbed Mechanisms*, ed. L. A. Cioffi, W. P. T. James, T. B. Van Itallie, pp. 45–55. New York: Raven
92. Krinsky, R., Lotter, E. C., Woods, S. C. 1979. Appetite suppression caused by CCK is diet-specific in VMH-lesioned rats. *Physiol. Psychol.* 7:67–69
93. Lamers, C., Harrison, A., Ippoliti, A., Walsh, J. 1979. Molecular forms of circulating gastrin in normal subjects and duodenal ulcer patients. *Gastroenterology* 76:1179 (Abstr.)
94. Landor, J. H. 1964. The effect of extragastric vagotomy on Heidenhain pouch secretion in dogs. *Am. J. Dig. Dis.* 9:256–62
95. Leander, S., Brodin, E., Hakanson, R., Sundler, F., Uddman, R. 1982. Neuronal substance P in the esophagus. Distribution and effects on motor activity. *Acta Physiol. Scand.* 115:427–35
96. Le Mangen, J. 1983. Body energy balance and food intake: a neuroendocrine regulatory mechanism. *Physiol. Rev.* 63:314–86
97. Liebling, D. S., Eisner, J. D., Gibbs, J., Smith, G. P. 1975. Intestinal satiety in rats. *J. Comp. Physiol. Psychol.* 89:955–65
98. Lin, T. M. 1975. Actions of gastrointestinal hormones and related peptides on the motor function of the biliary tract. *Gastroenterology* 69:1006–22
99. Long, R. G., Christofides, N. D., Fitzpatrick, M. L., McGregor, G. P., Bloom, S. R. 1980. Effects of motilin and somatostatin on gastric emptying and glucose tolerance. *Gastroenterology* 78:1210 (Abstr.)
100. Lotter, E. C., Krinsky, R., McKay, J. M., Treever, C. M., Porte, D. Jr., et al. 1981. Somatostatin decreases food intake of rats and baboons. *J. Comp. Physiol. Psychol.* 95:278–87
101. Lundberg, J. M. 1981. Evidence of coexistence of vasoactive intestinal polypeptide and acetylcholine in neurones of cat exocrine glands. *Acta Physiol. Scand.* 112(Suppl. 496):1–57
102. Lundberg, J. M., Tatemoto, K. 1982. Pancreatic polypeptide family (APP, BPP, NPY and PYY) in relation to sympathetic vasoconstriction resistant to alpha-adrenoceptor blockade. *Acta Physiol. Scand.* 116:393–402
103. Magnusson, I., Thulin, L. 1981. Effects of substance P and somatostatin on

choleresis in anaesthetized dogs. *Acta Chir. Scand.* 147:667–71

104. Maton, P. N., Selden, A. C., Fitzpatrick, M. L., Chadwick, V. S. 1984. Infusion of cholecystokinin octapeptide in man: relation between plasma cholecystokinin concentrations and gallbladder emptying rates. *Eur. J. Clin. Invest.* 14:37–41
105. McCullum, R. W., Walsh, J. H. 1979. Relationship between the lower esophageal sphincter pressure and serum gastrin concentration in Zollinger Ellison Syndrome and other clinical settings. *Gastroenterology* 76:76–81
106. McDonald, T. J., Nilsson, G., Vagne, M., Ghatei, M. A., Bloom, S. R., et al. 1978. A gastrin releasing peptide from the porcine nonantral tissue. *Gut* 19:767–74
107. McIntosh, C. H. S., Pederson, R. A., Koop, H., Brown, J. C. 1979. Inhibition of GIP-stimulated somatostatin like immunoreactivity by acetylcholine and vagal stimulation. In *Gut Peptides,* ed. A. Miyoshi, pp. 100–4. Amsterdam: Elsevier
108. McLaughlin, C. L., Baile, C. A. 1980. Decreased sensitivity of Zucker obese rats to the putative satiety agent cholecystokinin. *Physiol. Behav.* 25:543–48
109. Meeroff, J. C., Go, V. L. W., Phillips, S. F. 1975. Control of gastric emptying by osmolality of duodenal contents in man. *Gastroenterology* 68:1144–51
110. Meisenberg, G., Simmons, W. H. 1983. Minireview: Peptides and the blood brain barrier. *Life Sci.* 32:2611–23
111. Micevych, P. E., Go, V. L. W., Yaksh, T. L., Finkelstein, J. 1984. In vitro release of cholecystokinin from hypothalamus and frontal cortex of Sprague-Dawley, Zucker lean (Fa/−) and obese (fa/fa) rats. *Peptides* 5:73–80
112. Morgan, K. G., Schmalz, P. F., Go, V. L. W., Szurszewski, J. H. 1978. Effects of pentagastrin, G17 and G34 on the electrical and mechanical activities of canine antral smooth muscle. *Gastroenterology* 75:405–12
113. Moriarty, K., Hegarty, J. E., Tatemoto, K., Mutt, V., Christofides, N. D., et al. 1984. Peptide histidine isoleucine (PHI) inhibits water and ion absorption in the human jejunum. *Gastroenterology* 86:1118 (Abstr.)
114. Morley, J. E., Levine, A. S. 1983. The central control of appetite. *Lancet* 1:398–401
115. Morley, J. E., Levine, A. S. 1984. Neuropeptide Y potently induces ingestive behaviors after central administration. *Dig. Dig. Sci.* 29(Suppl.):55S (Abstr.)
116. Morley, J. E., Levine, A. S., Grace, M., Kneip, J. 1982. An investigation of the role of kappa opiate receptor agonists in the initiation of feeding. *Life Sci.* 31:2617–26
117. Mukhopadhyay, A. K., Johnson, L. R., Copeland, E. M., Weisbrodt, N. W. 1975. Effect of secretin on electrical activity of small intestine. *Am. J. Physiol.* 229:484–88
118. Mukhopadhyay, A. K., Thor, P. J., Copeland, E. M., Johnson, L. R., Weisbrodt, N. W. 1977. Effect of cholecystokinin on myoelectric activity of the small bowel of dogs. *Am. J. Physiol.* 232:E44–47
119. Nilsson, G., Simon, J., Yalow, R. S., Berson, S. A. 1972. Plasma gastrin and gastric acid responses to sham-feeding and feeding in dogs. *Gastroenterology* 63:51–59
120. Paintal, A. S. 1973. Vagal sensory receptors and their reflex effects. *Physiol. Rev.* 53:159–227
121. Pappas, T., Debas, H., Walsh, J. H., Tache, Y. 1984. Calcitonin gene-related peptide: A new neuropeptide that potently inhibits gastric acid secretion. *Dig. Dis. Sci.* 29(Suppl.):63S (Abstr.)
122. Poitras, P., Modigliani, R., Bernier, J.-J. 1980. Effect of a combination of gastrin, secretin, cholecystokinin, glucagon and gastric inhibitory polypeptide on jejunal absorption in man. *Gut* 21:299–304
123. Polak, J. M., Bloom, S. R. 1979. The hormones of the gastrointestinal tract. In *Scientific Basis of Gastroenterology,* ed. H. L. Duthie, K. G. Wormsley, pp. 71–111. Edinburgh: Churchill Livingstone
124. Polak, J. M., Bloom, S. R. 1983. Distribution of newly discovered regulatory peptides. *Biomed. Res. Suppl.* 4:7–23
125. Preshaw, R. M. 1973. Inhibition of pentagastrin stimulated gastric acid output by sham feeding. *Fed. Proc.* 32:410 (Abstr.)
126. Raptis, S. D., Dollinger, H. C., von Berger, L., Schlegal, W., Schroder, K. E., et al. 1975. Effects of somatostatin on gastrin secretion and gastrin release in man. *Digestion* 13:15–26
127. Rayford, P. L., Villar, H. V., Reeder, D. D., Thompson, J. C. 1974. Effect of GIP and VIP on gastrin release and gastrin secretion. *Physiologist* 17:319 (Abstr.)
128. Rodrigo, J., Polak, J. M., Fernandez, L., Ghatei, M. A., Mulderry, P. K., et al. 1985. CGRP immunoreactive sensory and motor nerves of the rat, cat and monkey oesophagus. *Gastroenterology.* In press

129. Roland, M., Berstad, A., Liavag, I. 1975. Effect of carbocholine and urecholine on pentagastrin stimulated gastric secretion in healthy subjects. *Scand. J. Gastroenterol.* 10:357–67
130. Saffouri, B., Weir, G. C., Bitar, K. N., Makhlouf, G. M. 1980. Gastrin and somatostatin secretion by perfused rat stomach. Functional linkage of antral peptides. *Am. J. Physiol.* 238:G495
131. Sarles, H., Dani, R., Prezelin, G., Souville, C., Figarella, C. 1968. Cephalic phase of pancreatic secretion in man. *Gut* 9:214–21
132. Sarr, M. G., Kelly, K. A. 1981. Myoelectric activity of the autotransplanted canine jejunoileum. *Gastroenterology* 81:303–10
133. Scarpignato, C., Micali, B., Vitulo, F., Zimbaro, G., Bertaccini, G. 1982. Inhibition of gastric emptying by bombesin in man. *Digestion* 23:128–31
134. Schaffalitzky de Muckadell, O. B., Fahrenkrug, J. 1978. Secretion pattern of secretin in man: regulation by gastric acid. *Gut* 19:812–18
135. Schaffalitzky de Muckadell, O. B., Fahrenkrug, J., Matzen, P., Rune, S. J., Worning, H. 1979. Physiological significance of secretin in the pancreatic bicarbonate response to a physiological increase in plasma secretin concentration. *Scand. J. Gastroenterol.* 14:85–90
136. Schneider, B. S., Monahan, J. W., Hirsch, J. 1979. Brain cholecystokinin and nutritional status in rats and mice. *J. Clin. Invest.* 64:1348–56
137. Schultzberg, M., Hokfelt, T., Lundberg, J. M. 1982. Neuronal coexistence of amines and peptides. *Br. Med. Bull.* 38:309–13
138. Scratcherd, T. 1981. The control of pancreatic exocrine secretion. In *Topics in Gastroenterology, 9*, ed. D. P. Jewell, E. Lee, pp. 193–213. Oxford: Blackwell Scientific
139. Shea-Donohue, P. T., Adams, N. A., Dubois, A. 1981. The role of endogenous opiates in the gastric emptying and secretory response to various calorie meals. *Z. Gastroenterol.* 19:406
140. Singer, M. V., Solomon, T. E., Wood, J., Grossman, M. I. 1980. Latency of pancreatic enzyme response to intraduodenal stimulants. *Am. J. Physiol.* 238:G23–29
141. Skrabanek, P., Powell, D. 1977. Substance P. In *Annual Research Reviews*, ed. P. Skrabaneck, D. Powell, 1:69–101. Edinburgh: Churchill Livingstone
142. Smith, G. P. 1983. The peripheral control of appetite. *Lancet* 2:88–90
143. Smith, G. P. 1983. The role of the gut in the control of food intake. *Viewpoints Dig. Dis.* 15:1–4
144. Smith, G. P., Gibbs, J., Jerome, C., Pi-Sunyer, F. X., Kissileff, H. R., et al. 1981. The satiety effect of cholecystokinin; a progress report. *Peptides* 2(Suppl. 2):57–59
145. Smith, G. P., Jerome, C., Gibbs, J. 1981. Abdominal vagotomy does not block the satiety effect of bombesin in the rat. *Peptides* 2:409–11
146. Soares, E. C., Zaterka, S., Walsh, J. H. 1977. Acid secretion and serum gastrin at graded intragastric pressure in man. *Gastroenterology* 72:676–79
147. Soll, A. H., Walsh, J. H. 1979. Regulation of gastric acid secretion. *Ann. Rev. Physiol.* 41:35–53
148. Spiller, R. C., Trotman, I. F., Higgins, B. E., Ghatei, M. A., Grimble, G. K., et al. 1984. The ileal brake—inhibition of jejunal motility after ileal fat perfusion in man. *Gut* 25:365–74
149. Stacher, G., Steinringer, H., Schmierer, G., Schneider, C., Winklehner, S. 1982. Cholecystokinin octapeptide decreases intake of solid food in man. *Peptides* 3:133–36
150. Stening, G. F., Grossman, M. I. 1969. Potentiation of the cholecystokinetic action of CCK by secretin. *Clin. Res.* 17:528 (Abstr.)
151. Strunz, U. T., Grossman, M. I. 1978. Effects of intragastric pressure on gastric emptying and secretion. *Am. J. Physiol.* 235:E552–55
152. Taché, Y. F., Brown, M. R. 1981. Central nervous system control of gastric secretion: role of neuropeptides. See Ref. 17, pp. 471–75
153. Tatemoto, K. 1982. Isolation and characterisation of peptide YY (PYY) a candidate gut hormone that inhibits pancreatic exocrine secretion. *Proc. Natl. Sci. USA* 79:2514–18
154. Taylor, I. L., Walsh, J. H., Carter, D. C., Wood, J., Grossman, M. I. 1979. Effects of atropine and bethanecol on bombesin stimulated release of pancreatic polypeptide and gastrin in dog. *Gastroenterology* 77:714–18
155. Thomas, P. A., Schang, J.-C., Kelly, K. A., Go, V. L. W. 1979. Can endogenous gastrin inhibit canine interdigestive gastric motility? *Gastroenterology* 78:716–21
156. Thompson, J. C., ed. 1977. *Gastrointestinal Hormones. A Symposium.* Austin: Univ. Texas Press
157. Thompson, J. C., Reeder, D. D., Buchman, H. H., Becker, H. D., Brandt, E. R. S. Jr. 1972. Effect of secretin on circulating gastrin. *Ann. Surg.* 176:384–93

158. Thomsen, O. O. 1984. Mechanism and regulation of hepatic bile production. With special reference to the bile acid-independant canalicular bile formation. *Scand. J. Gastroenterol.* 19(Suppl. 97):1–52
159. Thor, K., Rosell, S., Rokaeus, A., Kager, L. 1982. (Gln^4)neurotensin changes the motility pattern of the duodenum and proximal jejunum from a fasting-type to a fed-type of activity. *Gastroenterology* 83:569–74
160. Thulin, L., Hellgren, M. 1976. Choleretic effect of vasoactive intestinal polypeptide. *Acta Chir. Scand.* 142:235–37
161. Turnberg, L. A. 1983. Control of intestinal secretion. *Scand. J. Gastroenterol.* 18(Suppl. 87):85–89
162. Uddman, R., Alumets, J., Edvinsson, L., Hakanson, R., Sundler, F. 1978. Peptidergic (VIP) innervation of esophagus. *Gastroenterology* 75:5–8
163. Uddman, R., Alumets, J., Hakanson, R., Sundler, F., Walles, B. 1980. Peptidergic (enkephalin) innervation of the mammalian esophagus. *Gastroenterology* 78:732–37
164. Uvnas, B., Wallensten, K., Anderson, H. 1977. Effect of atropine and methiamide on vagally induced gastric acid secretion and gastrin release in anaesthetized cats. *Acta Physiol. Scand.* 99:496–502
165. Valenzuela, J. E., Defilippi, C. 1981. Inhibition of gastric emptying in humans by secretin, the ocapeptide of cholecystokinin and intraduodenal fat. *Gastroenterology* 81:898–902
166. Valenzuela, J. E., Lamers, C. B., Buga, G., Modlin, I. M., Walsh, J. H. 1979. Comparative study of circulating cholecystokinin and CCK octapeptide as stimulants of pancreatic secretion in man. *Gut* 20:A925 (Abstr.)
167. Vatn, M. H., Schrumpf, E., Myren, J. 1975. The effect of carbachol and pentagastrin on the gastric secretion of acid, pepsin and intrinsic factor in man. *Scand. J. Gastroenterol.* 10:55–58
168. Deleted in proof
169. Walsh, J. H. 1981. Gastrin. See Ref. 17, pp. 163–70
170. Walsh, J. H., Richardson, C. T., Fordtran, J. S. 1975. pH dependence of acid secretion and gastrin release in normal and ulcer subjects. *J. Clin. Invest.* 55:462–68
171. Wienbeck, M., Ercenbrecht, J. 1982. The control of gastrointestinal motility by GI hormones. *Clin. Gastroenterol.* 11:523–43
172. West, D. B., Fey, D., Woods, S. C. 1984. Cholecystokinin persistently suppresses meal size but not food intake in free-feeding rats. *Am. J. Physiol.* 246:R776–87
173. White, T. T., Lundh, G., Magee, D. F. 1960. Evidence for the existence of a gastropancreatic reflex. *Am. J. Physiol.* 198:725–28
174. Wingate, D. L. 1981. Backwards and forwards with the migrating complex. *Dig. Dis. Sci.* 26:641–66
175. Woods, S. C., West, D. B., Stein, L. J., McKay, L. D., Lotter, E. C., et al. 1981. Peptides and the control of meal size. *Diabetologia* 20:305–13
176. Wormsley, K. G. 1979. A comparison of the response to secretin, pancreozymin and a combination of these hormones in man. *Scand. J. Gastroenterol.* 4:413–17
177. Wright, N. A. 1981. Regulation of growth by peptides. See Ref. 17, pp. 521–29
178. Zwick, R., Bowes, K. L., Daniel, E. E., Sarna, S. K. 1976. Mechanism of action of pentagastrin on the lower esophageal sphincter. *J. Clin. Invest.* 57:1644–51