Physiology of Gastrin

PAUL H. JORDAN, JR., M.D., Houston, Texas
RAUL GARCIA-RINALDI, M.D., Houston, Texas

In 1902, Bayliss and Starling [*1*] discovered that external pancreatic secretion is excited by a chemical stimulant, secretin, which is released from the intestinal mucosa upon contact with foodstuffs or with acid. At the time of this discovery, it was known that peptones within the stomach are a powerful stimulant of gastric secretion. Referring to the work of Bayliss and Starling, Edkins [*2*] drew an analogy between pancreatic secretion and gastric secretion. He speculated that absorption of foodstuffs from the stomach, which was thought to occur in the pyloric gland area, released a chemical substance from gastric mucosa which had the capacity to stimulate parietal cells.

It is of interest that the first two hormones postulated should require nearly sixty years to purify, and in the case of gastrin, fifty years elapsed before the critical experiment performed by Grossman, Robertson, and Ivy [*3*] provided proof for the physiologic existence of the gastrin mechanism. It is of further interest that although these two hormones exert their primary effects on different organs and were therefore thought to act quite independently of one another, they are in fact quite interrelated in their actions. In addition to stimulating gastric secretion, gastrin is known to have a variety of actions including stimulation of pancreatic secretion. Although secretin has as its primary action the stimulation of pancreatic secretion, it also inhibits gastrin-stimulated gastric secretion.

The evolution of knowledge of the physiology of gastrin was retarded by the controversy over whether gastrin was histamine. Komarov [*4,5*] attempted to settle the issue by devising an extraction method for gastrin which would separate it from histamine. Because his preparations were not always active, it was not until 1961, when Gregory and Tracy [*6*] purified and shortly thereafter synthesized the hormone, that its existence was absolutely established. Even after the reality of gastrin as a separate entity was known, there was resistance in disassociating its action from histamine. Babkin's [*7*] original theory that histamine is the final link in gastric secretion has been reproposed. It was suggested that the function of gastrin is histamine release [*8*], although the evidence for this hypothesis is not convincing [*9*]. Present information indicates that gastrin acts on one of the cellular elements of the parietal cell, thereby activating it to secrete.

From the Departments of Surgery, Baylor University College of Medicine and Veterans Administration Hospital, Houston, Texas.

Release of Gastrin

Heidenhain [*10*] demonstrated that food placed in the main part of the stomach of dogs caused their miniature stomachs (Heidenhain pouches) to secrete gastric juice. Gross [*11*] showed that this did not occur if the pyloric gland area was separated from the rest of the stomach and was not in contact with food. Pavlov [*12*] and associates were of the opinion that gastric secretion resulting from contact of the pyloric gland area with food was due to local reflexes since the effect was present after vagotomy but was abolished by atropine. However, Pavlov [*12*] did acknowledge the possibility proposed by Edkins that digestive products in the stomach release a chemical substance from the mucosa which is distributed by the blood to the gastric glands resulting in gastric secretion. It remained for Uvnäs [*13*] in 1942 to show that in addition to release of gastrin by chemical stimuli, vagal impulses to the pyloric gland area are also capable of releasing gastrin, thus demonstrating that the regulation of gastric secretion by the pyloric gland area is under neurohumoral influences.

The conclusions drawn by Uvnäs relative to

the vagal release of gastrin from the pyloric gland area did not go unchallenged. Oberhelman, Rigler, and Dragstedt [14] thought that release of gastrin after vagal stimulation by hypoglycemia resulted from the pressure effect upon the mucosa produced by muscular contraction. Grossman [15] was critical of Uvnäs' hypothesis and was of the opinion that gastrin was not released by vagal stimulation. Subsequently, Thein and Schofield [16], Olbe [17], Jordan and de la Rosa [18], and others confirmed Uvnäs' observations that gastrin is released by vagal stimulation. In addition to experiments in which vagal stimulation was produced by hypoglycemia, studies were also performed using sham feeding as the vagal stimulant. Since sham feeding does not cause pyloric contraction, activation of the gastrin mechanism could not be attributed to this factor.

Gastrin is also released without there being any nervous connections to the pyloric gland area. It is known that various secretagogues such as meat extract, alcohol, and acetylcholine as well as mechanical distention of the antrum stimulate gastrin release [19]. It remained, however, for Grossman [3], using a dog with a Heidenhain pouch and a transplanted antral pouch stimulated by distention, to demonstrate conclusively that the gastrin mechanism exists in the absence of nervous pathways between the pyloric gland area and the fundic gland area.

Since the time of Pavlov and Edkins, it has been convenient to consider the cephalic phase of gastric secretion as centrally mediated by the vagus nerves, resulting in direct stimulation of the parietal cell, and to consider the gastric phase as mediated by the local release of the hormone gastrin, resulting in indirect stimulation of the parietal cell. That the control of gastric secretion is not so simple was suggested first by Uvnäs [13] who showed that central vagal stimulation exerts a dual effect on acid-secreting cells; first, there is the direct stimulation of the parietal cells, and second, there is the indirect effect which results from the vagal release of gastrin. The gastric phase of gastric secretion also has a dual mechanism mediated by cholinergic reflexes. Grossman [20] showed that distention of the vagally innervated acid secreting portion of the stomach after resection of the pyloric gland area resulted in gastric secretion. The high pepsin content of the juice produced in this manner supported his view that secretion was in response to a vagovagal reflex. Direct stimulation of parietal cells by distention was also demonstrated to occur but to a lesser degree after vagal denervation [21]. This was thought to represent a local cholinergic reflex. Similarly, Grossman postulated that the hormonal stimulation of gastric secretion which results during the gastric phase is the result of local and long reflexes similar to those described for the direct component of the gastric phase. That local neural reflexes are responsible for the release of gastrin after local stimuli is suggested by the findings that topical anesthetics applied to the mucosa prevent responses to such stimuli [22] but do not interfere with gastrin released by acetylcholine itself [23].

This unified hypothesis shows how parietal cell stimulation and gastrin release occur as the result of cholinergic effects in both the cephalic and gastric phases of gastric secretion.

Inhibition of Gastrin Release

Pavlov [12] described a form of autoregulation on the part of the stomach which controls the secretion of hydrochloric acid. He reported that the accumulation of acid within the stomach prevented further secretion of gastric juice. Pavlov further described the inhibitory effect of intragastric fat on gastric secretion and attributed the inhibition to a reflex initiated by the fat as it moves into the intestine. Woodward et al. [22], utilizing dogs with isolated innervated antral pouches, demonstrated that acid perfusion of the pyloric gland area mucosa inhibited gastrin-stimulated gastric secretion by prevention of gastrin release. Gastrin release by secretagogues within the antrum decreased as antral pH decreased, until gastric secretion was abolished at a pH of 1.5 [24].

Prior to the findings of Woodward et al. [22] the vagal release of gastrin proposed by Uvnäs [13] was questioned because vagal stimulation by sham feeding failed to stimulate secretion from a Heidenhain pouch. Later, Thein and Schofield [16] confirmed Uvnäs' contention that vagal impulses released gastrin when they showed that vagal stimulation resulted in a secretory response from a Heiden-

hain pouch if acid was excluded from the antrum by the preparation of an innervated isolated antrum.

The mechanism by which antral acidification inhibits release of gastrin is still in question. The inhibitory effect of low pH in the pyloric gland area on gastric secretion initiated by chemical stimulation of the antrum may result from interference with gastrin release [*25*] or the release of a chalone which inhibits the action of gastrin [*26–28*]. Evidence is in favor of antral acidification inhibiting the release of gastrin rather than producing an antisecretory hormone. This view is supported by Gillespie and Grossman [*29*] who demonstrated that acidification of the antrum inhibited gastric secretion from a Heidenhain pouch stimulated by perfusion of the antrum with acetylcholine but had no effect on gastric secretion from a Heidenhain pouch produced by intravenous administration of gastrin.

Perfusion of the antrum with topical anesthetics inhibits gastrin release produced by meat extracts, which suggests that an intramucosal nervous pathway is concerned with the release of gastrin. Stimulation of gastric secretion by perfusion of the antrum with acetylcholine is inhibited by antral acidification but unaffected by cocainization. When the antrum is cocainized and irrigated with acidified acetylcholine, acid secretion is inhibited. These studies indicate that acetylcholine stimulates the gastrin-producing cell directly. Failure of cocaine to interfere with the inhibition of acetylcholine by acid suggests that acid must exert its inhibitory effect at the level of the gastrin-producing cell and does not support the possibility that an intramucosal nervous pathway is concerned with the inhibitory effect of antral acidification. If acid does act at the level of the gastrin-producing cell, it can be presumed that this cell is located at the mucosal surface since it seems unlikely that a pH as low as 1.5 can exist within the mucosa.

An appreciation of the inhibitory effect of an acid environment on the release of gastrin from the pyloric gland area has lead to the recognition and understanding of an important problem in the operative management of duodenal ulcer patients. Recurrent marginal ulcer may result from isolation of the pyloric gland area from contact with acid either intentionally by the exclusion operations of Finsterer and Devine or unintentionally during a routine gastric resection when the pylorus is unrecognized and transection of the stomach occurs through the antrum rather than the pylorus. Regurgitation of food through the afferent limb and into the residual antrum has been demonstrated under these conditions [*30*].

It seems likely that regurgitated food in the presence of the neutralizing effect of alkaline bile and pancreatic juice exert a gastrin-releasing action uninhibited by the presence of acid. That such a mechanism is, in fact, the cause for the high recurrence rate after exclusion operations has been adequately documented [*31*]. Therefore the surgeon, when operating on a patient for marginal ulcer, should inspect the duodenal stump for retained antrum.

At about the same time, Wilhelmj, McCarthy, and Hill [*32*], Day and Webster [*33*], and Griffiths [*34*] independently reported that hydrochloric acid in the duodenum inhibits the intestinal phase of gastric secretion. Code and Watkinson [*35*] reported that duodenal acidification inhibited gastric secretion only if the vagal innervation of the gastric mucosa was intact. Later, Andersson [*36*] in a series of studies showed that acid in the duodenum inhibited fasting and postprandial secretion in Heidenhain and Pavlov pouches as well as gastric secretion resulting from insulin hypoglycemia.

To clarify the mode of action of duodenal acidification on inhibition of gastric secretion, Andersson [*37*] demonstrated that gastric secretion stimulated by intravenous injection of gastrin was significantly inhibited by duodenal acidification. This suggests that either by a humoral and/or a nervous reflex, acid in the duodenum exerts its effect at the parietal cell level.

First Greenlee et al. [*38*] and later others [*39–41*] showed that intravenous secretin inhibited gastric secretion stimulated by meat extract, histamine, and gastrin, but not that stimulated by insulin hypoglycemia [*38,39*]. Johnson and Grossman [*42*] reported that the administration of a physiologic dose of secretin produced the same degree of inhibition of gastric secretion that occurred with duodenal acidification.

Purification and Synthesis of Gastrin

From the time Edkins proposed his hypothesis of gastrin until Gregory and Tracy purified

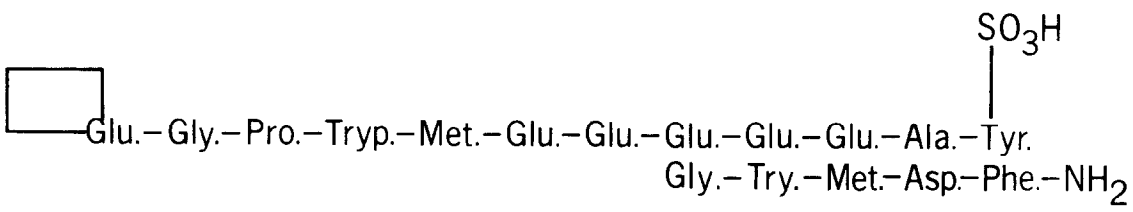

Fig. 1. The structure of hog gastrin II.

gastrin, there was considerable controversy over its actual existence. Preparations of gastrin were attempted by numerous investigators with varying degrees of success. An extract prepared by Harper and used by Gregory was found inactive [*43*] probably, but not realized at the time, because of the inhibitory effect of gastrin when given intravenously in large doses [*44*].

Gregory then decided to prepare his own gastrin and as a result evolved a new method of extraction which provided a nonhomogenous, but sufficiently pure material that it could be given subcutaneously to human subjects without side effects [*45,46*]. With further studies and purification, Gregory and Tracy [*47*] were able to report that there are two gastrins, gastrin I and gastrin II. The amino acid sequence of gastrin was reported by Gregory's colleagues in 1964 [*48,49*]. In the same year, Gregory and Tracy [*50*] reported on the synthesis of gastrin. Both gastrins are polypeptides with seventeen amino acid residues and are the same except for a sulfate group attached to tyrosine. (Fig. 1.) The similarity between the physiologic actions produced by endogenously liberated antral hormone and the peptides prepared by Gregory and his group suggest that the peptides are closely related to, if they are not actually the hormone which is liberated into the blood when the pyloric gland area is stimulated.

The only difference between the gastrins of various species studied thus far consist of substitutions of one or two of the seventeen amino acid residues. All species studied have the same C-terminal tetrapeptide amide: -Try-Met-Asp-Phe-NH_2. It is remarkable that this portion of the molecule can produce all of the gastrointestinal effects of gastrin. It has all the biological activities of the full molecule although it is much less potent than the whole molecule. The amide on the C-terminal phenylalanine is indispensable for removal of this group results in nearly complete loss of the molecule's activity. Smaller fragments have no biological activity.

In addition to synthesis of porcine and human gastrin, many smaller peptides related to gastrin have been synthesized but the compound most readily available and widely used for human and animal studies is the β-alanyl derivative of the C-terminal tetrapeptide amide: β-Ala-Try-Met-Asp-Phe-NH_2, otherwise known as betagastrin. The drug has been widely used in a cooperative study in England for stimulation of maximal gastric secretion and the results were reported by Abernathy et al. [*51*]. They demonstrated that it serves as well as histamine for this purpose and is without side effects. There has been no evidence that it is superior to the analog of histamine, betazole hydrochloride.

Thus far, no specific antagonist of gastrin has been found among the analogs that have been synthesized and studied. Compound SC-15396, the most recent drug investigated for possible antigastrin properties, was shown to be a powerful inhibitor in dogs of gastric secretion stimulated by endogenous gastrin, exogenous gastrin, and histamine and vagal stimulation with 2-deoxyglucose (2-DG) [*52,53*]. The evidence is not clear whether the antisecretory effect of this drug is a nonspecific gastric secretory inhibitor or whether it is a specific antigastrin which suppresses histamine and vagal stimulation of gastric output by virtue of its antigastrin properties which thus prevent potentiation of histamine and cholinergic stimuli by gastrin. Since SC-15396 inhibits 2-DG secretion in dogs without an endogenous source of gastrin, the material is most likely a nonspecific inhibitor rather than a true antigastrin [*52*].

Evidence has been present for the existence of an intestinal "gastrin" but whether this has the same chemical structure of gastric gastrin is unknown. Cholecystokinin-pancreozymin which has been shown to stimulate gastric secretion [*54*] and to have a close chemical re-

semblance to the C-terminal sequence of gastrin [55] may be the intestinal "gastrin."

Potentiating Action of Gastrin

In addition to the cholinergic mechanism releasing gastrin, there is potentiation between gastrin and cholinergic stimuli. Potentiation occurs when the response between two drugs is greater than their additive effects and can be shown to exist between drugs when the maximal response to two agents given together is greater than the maximal response to either agent given alone. When gastrin and cholinergic stimuli act simultaneously on acid-secreting glands, as occurs in the intact stomach with eating, acid secretion is greater than would be expected to occur on the basis of simple addition of the responses to their individual actins. Gillespie and Grossman [56] demonstrated that combinations of gastrin extracts and cholinergic drugs and gastrin and histamine satisfy the criteria for potentiation. Evidence suggests that the tonic activity of the vagi which by itself does not result in gastric secretion causes sufficient background of cholinergic activity to produce potentiation with gastrin and with histamine. This explains the observation that denervated gastric mucosa is less sensitive to all stimuli including gastrin than is innervated mucosa. Conversely, Olbe [17] and Jordan and de la Rosa [18] demonstrated potentiation between the direct cholinergic stimulation of the acid-secreting glands after vagal stimulation and the threshold dose of gastrin released by vagal stimulation. The marked acid secretion resulting from synergism between these two stimuli, which when acting alone produce small responses, emphasizes the important role of vagally-released gastrin which by itself appears to have an insignificant secretory effect.

It has long been recognized by surgeons that resection of the pyloric gland area of the stomach in patients with duodenal ulcer is an operation associated with a high incidence of marginal ulcer. These observations appear paradoxical if the response of the parietal cells to vagal stimulation is dependent on potentiation by gastrin. The explanation for this observation may be that increased vagal activity playing on an increased parietal cell mass is adequate to produce hypersecretion in man and that potentiation of cholinergic activity by gastrin is unnecessary to produce the degree of acid secretion required for ulceration. On the other hand, Jordan [57] showed in dogs that the intestinal phase of gastric secretion, presumably the result of an intestinal "gastrin," exerted a synergistic effect on the gastric secretory rate after vagal stimulation by sham feeding. The relevance of this finding to marginal ulceration after antrectomy in man is unknown.

Other Physiologic Actions of Gastrin

In 1959, Blair et al. [58] reported that an extract of the pyloric gland area of the stomach, presumably gastrin, was capable of stimulating pancreatic secretion. After the availability of pure natural and synthetic gastrins, it was recognized that the pancreatic secretory effect of the pyloric gland extract represented another function of gastrin. Indeed, gastrin has a wide variety of actions which Grossman [59] divided into two categories: (1) "physiologic" actions if they are reproducible by endogenous release of gastrin and if they occur with the administration of intravenous doses of gastrin which are submaximal for acid secretion; and (2) "pharmacologic" actions if they are seen only with large doses of gastrin given rapidly by the intravenous route and not reproducible by endogenous release of gastrin.

The "physiologic" actions of gastrin include secretion of water, electrolytes, and enzymes by the stomach [60] and pancreas [61], contraction of the stomach [62], and stimulation of bile flow [63]. This spectrum of activities assigned to gastrin has been established for the dog but its relevance in man in each case has not been determined. The "pharmacologic" actions include inhibition of gastric secretion [64] and contraction of the intestine [50] and gallbladder [65]. The inhibition of gastric secretion by large doses of gastrin which has been demonstrated in dogs does not occur in man, rat, or cat [66]. If this phenomenon occurred in man, it might be expected that in patients with metastatic Zollinger-Ellison tumors their own gastric secretion would eventually be inhibited. This observation has never been made.

Production of Antibodies to Gastrin

The obvious need for a method of gastrin as-

say has been approached by two methods, the bioassay [67,68] and the immunoassay methods [69–71]. Neither method has yet been developed to the point of sufficient reliability to be adopted for general use. The bioassay methods have been found inadequate because patients may have ulcerogenesis with a high level of circulating gastrin which is below the test's lower limits of sensitivity.

Investigators have encountered considerable difficulty in their attempts to prepare antibodies to pure gastrin. Antibodies have been prepared against impure gastrin that cross react with pure gastrin [69]. Antibodies have also been made against the C-terminal tetrapeptide amide of gastrin conjugated to a protein which reacts to the whole molecule of pure gastrin [72]. The antibodies elicited in response to immunization with gastrin C-terminal tetrapeptide amide conjugated to bovine γ-globulin cross react and bind with cholecystokinin-pancreozymin as well as C-terminal tetrapeptide and gastrin [73]. These findings are consistent with the evidence presented by Mutt and Jorpes [55] that the carboxyl-terminal portions of gastrin and cholecystokinin-pancreozymin are identical.

Although the production of gastrin antibodies remains a problem for most investigators, McGuigan [74] has reported that the sensitivity of his immunoassay method is 5 μg., a level of sensitivity expected to be adequate to measure physiologic levels of gastrin in human serum. Stremple and Meade [71] have also successfully produced antibodies. In spite of any cross reaction with cholecystokinin-pancreozymin, they were able to divide human sera according to the level of circulating gastrin into those that were normal and those with the hypergastrinism of the Zollinger-Ellison syndrome.

There are two clinical conditions in which the excess production of gastrin is known to play an important role and in which the measurement of gastrin is important. The first, which was referred to previously, is that of a marginal ulcer that results from the exclusion of the antrum after gastric resection and a Billroth II reconstruction. Isolation of the antrum in an alkaline environment permits uncontrolled gastrin release resulting in hypersecretion and stomal ulcer formation. Every patient reoperated upon for a marginal ulcer in whom Billroth II reconstruction has been carried out should be examined for possible retained antrum. In most instances, if resection has otherwise been adequate and/or vagotomy has been performed, removal of the antrum will insure against recurrent ulcer.

The second disease in which gastrin plays an important role was described by Zollinger and Ellison [75] in 1955. This entity, which is associated with benign or malignant non-beta islet cell lesions of the pancreas and a severe ulcer diathesis from hypersecretion of gastric juice, is known to result from an abnormal production of gastrin by the tumor [76,77] that is identical in amino acid composition to human antral gastrin [78]. After the discovery that gastric hypersecretion in patients with Zollinger-Ellison syndrome results from the unregulated production of gastrin by the pancreatic tumor, a search was begun for a gastric secretory stimulant in normal pancreas but this stimulant was found lacking in most studies [79].

The availability of highly specific antibodies may be helpful in localization of the cell of origin of gastrin. By using fluoresceinated antibodies to human gastrin I, McGuigan [80] already has claimed to have localized gastrin within mucosal cells of the antrum of man and hog. In those studies, immunofluorescence was restricted to cytoplasmic granules in differentiated, interspersed mucosal cells present along the course of the pyloric gland area. Eventually, the availability of antibodies may even make it possible to establish the validity of Dragstedt's theory of hyperfunction of the antrum as the cause of gastric ulcer.

Conclusion

In the years that have passed since Edkins proposed his theory for gastrin in 1905, this area of gastrointestinal physiology has become an exciting field of research and studies have gained tremendous momentum in the recent years since Gregory and his colleagues purified and synthesized gastrin. With the importance of gastrin for the control of gastric secretion firmly established and its role in the pathogenesis of peptic ulcer recognized by all clinicians, it is now necessary to establish where gastrin is made, how it can be measured, and how we can suppress its release or inhibit its action. In the words of Gregory, "there are,

we can be sure, some exciting pages still to be turned in 'The Gastrin Story!' "[43].

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