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Research Article

Bolus injections of gastrin or pentagastrin (PG) cause a marked elevation in lower esophageal sphincter pressure (LESP), and it has been suggested that serum gastrin concentration is the main physiological and pathophysiological regulator of LESP. We evaluated this hypothesis by measuring LESP and gastric acid secretion simultaneously in normal subjects during continuous infusion of PG (0.004-12 mg/kg per h), since continuous infusion of a hormone probably simulates physiological hormone release better than bolus injection. In groups of 8-13 subjects there was no statistically significant increase in average LESP with any of seven PG infusion rates. However, a bolus of PG superimposed on the continuous infusion of PG resulted in a 20-mm Hg increase in LESP. Examination of results in individual subjects suggested that PG by infusion might be stimulating LESP in some subjects and inhibiting it in others. Therefore, individual dose-response studies were performed in two normal subjects. These revealed that 0.9 mg/kg per h PG by infusion elevated LESP by 10-12 mm Hg. This dose of PG also elicited maximal rates of gastric acid secretion. In one of the subjects an infusion of PG calculated to give one-half maximal acid secretion (D50) elevated LESP by 8 mm Hg; in the other the PG-D50 for acid secretion had no effect on sphincter pressure. Infusion of smaller amounts of PG had [...]

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Effect of Continuous Infusion of Pentagastrin on Lower Esophageal Sphincter Pressure and Gastric Acid Secretion in Normal Subjects

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ABSTRACT Bolus injections of gastrin or penta-gastrin (PG) cause a marked elevation in lower esophageal sphincter pressure (LESP), and it has been suggested that serum gastrin concentration is the main physiological and pathophysiological regulator of LESP. We evaluated this hypothesis by measuring LESP and gastric acid secretion simultaneously in normal subjects during continuous infusion of PG (0.004–12 $\mu\text{g}/\text{kg}$ per h), since continuous infusion of a hormone probably simulates physiological hormone release better than bolus injection. In groups of 8–13 subjects there was no statistically significant increase in average LESP with any of seven PG infusion rates. However, a bolus of PG superimposed on the continuous infusion of PG resulted in a 20-mm Hg increase in LESP. Examination of results in individual subjects suggested that PG by infusion might be stimulating LESP in some subjects and inhibiting it in others. Therefore, individual dose-response studies were performed in two normal subjects. These revealed that 0.9 $\mu\text{g}/\text{kg}$ per h PG by infusion elevated LESP by 10–12 mm Hg. This dose of PG also elicited maximal rates of gastric acid secretion. In one of the subjects an infusion of PG calculated to give one-half maximal acid secretion (D_{50}) elevated LESP by 8 mm Hg; in the other the PG- D_{50} for acid secretion had no effect on sphincter pressure. Infusion of smaller amounts of PG had no effect on LESP, even though gastric acid secretion was stimulated submaximally.

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Thus, the parietal cells are more sensitive than the lower esophageal sphincter to the effect of PG by infusion. We conclude that PG by continuous infusion elevates LESP to only a modest degree (compared with the contraction that occurs after bolus injections of PG) and that the contraction occurs only within a narrow dose range between the D_{50} and D_{100} for acid secretion. Higher doses cause transient relaxation of LESP.

Additional studies showed that basal LESP varied between 16 and 71 mm Hg in two subjects studied on 29 separate occasions, but there was no correlation with basal acid secretion. This suggests that the wide day-to-day fluctuations in basal LESP are not due to changing concentrations of gastrin in serum. The results of these experiments cast doubt on the hypothesis that serum gastrin concentration is the major determinant of LESP.

INTRODUCTION

Several observations suggest that lower esophageal sphincter pressure (LESP)¹ is under the control of serum or tissue gastrin concentration. First, injections of gastrin or pentagastrin (PG) produce a marked increase in LESP (1–6). Second, physiological events which cause or supposedly cause endogenous gastrin release are associated with a rise in LESP. These include ingestion of a protein-rich meal (1, 2, 7), alkalization of the stomach (2, 8), and deacidification of the stomach (6, 8). Third, maneuvers that supposedly decrease en-

¹Abbreviations used in this paper: LES, lower esophageal sphincter; LESP, lower esophageal sphincter pressure; PG, pentagastrin.

ogenous gastrin release are associated with a fall in LESP. These include infusion of highly acid material into the stomach (2-4, 6, 8), ingestion of a protein meal that has been previously acidified to pH 1.5 (7), and intravenous injection of gastrin antiserum (5).

On the basis of these results it has been concluded that gastrin plays the major role in maintenance of resting LESP (3, 5, 9) and in increasing LESP under conditions where gastroesophageal reflux might otherwise occur (1, 2, 7). Furthermore, hypersensitivity to endogenous gastrin has been proposed as the cause of increased sphincter pressure in achalasia (4), and defective endogenous release has been proposed as the cause of sphincter incompetence in patients with reflux esophagitis (6). It has also been suggested that changes in sphincter pressure may be utilized to monitor endogenous gastrin activity (7) and that LESP is a more precise measure of circulating gastrin than radioimmunoassay (10).

In previous studies on the effect of gastrin or PG on LESP the hormones have been given almost exclusively by intravenous injection as a bolus or by subcutaneous administration. If gastrin is an important physiological stimulant of LESP, one would expect that continuous infusion of gastrin or PG would also increase LESP. However, the effect of continuous infusion of PG or gastrin on LESP has not been previously studied in detail. We have therefore measured the effect of a continuous 1-h infusion of PG on LESP and correlated this with the acid secretory response by the parietal cells of the stomach. We sought answers to two main questions. First, does the lower esophageal sphincter (LES) contract in response to a continuous infusion of PG, and if so, is the contraction transient, as it is after a bolus of PG, or does it last throughout the length of the infusion? And second, assuming that the sphincter contracts to a continuous infusion of PG, what is the relative sensitivity of the LES muscle and the gastric parietal cells to PG infusion? These studies were performed in normal human subjects using a wide range of PG infusion rates, from a dose so low that it did not increase gastric acid secretion to a dose that is higher than that required to elicit maximal acid secretion rate. In addition, we determined the correlation between unstimulated LESP and gastric acid secretion (i.e., with saline rather than PG infusion).

METHODS

Subjects. Studies were done on normal men and women who did not have any known disorder of the gastrointestinal tract. None of the subjects had any clinical symptoms of esophageal reflux. All subjects were studied after an overnight fast and in the supine position. No drugs of any kind were given for 12 h before the study. None of the subjects were taking anticholinergic drugs, tranquilizers, or barbiturates.

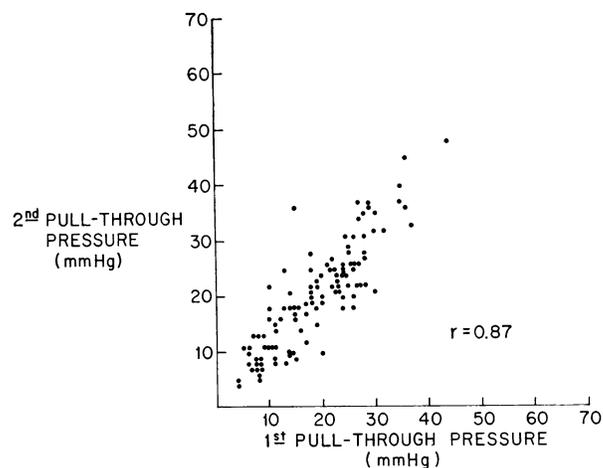


FIGURE 1 Correlation of two consecutive pull-through measurements of the LESP done within 4 min. The 13 subjects received an intravenous saline infusion.

Manometric recording system. Respiration and swallowing were monitored by a belt pneumograph. A single water-filled polyvinyl tube was used for measuring LESP. This tube had an internal diameter of 1.7 mm and a lateral orifice that was 1.5 mm in diameter. The tube was perfused with saline at a rate of 0.76 ml/min by means of a Harvard infusion pump (Harvard Apparatus Co., Inc., Millis, Mass.). A Statham transducer (model P23Db, Statham Instruments, Inc., Oxnard, Calif.), and either a recorder (Electronics for Medicine Inc., White Plains, N. Y.) or a Physiograph (Narco Bio-Systems, Inc., Houston, Tex.) were used for pressure measurements.

The pressure recording tube was mounted with tetrahydrofuran to a 16-Fr polyvinyl sump tube (Anderson Products, Inc., Oyster Bay, N. Y.) that was, in turn, used for removing gastric secretions. The opening of the pressure recording tube was 15 cm from the end of the sump tube. The combined outside measurement of the two-tube assembly was 4.5×6.5 mm.

Gastric secretion. Gastric contents were removed by suction to the sump tube, which was positioned fluoroscopically in the antrum of the stomach. Hydrogen ion concentration was measured by the method of Moore and Scarlata (11).

Experimental protocol. The study was divided into three parts. First, isotonic saline was infused intravenously for a control period of 30 min. During the second period, PG² was infused intravenously for 1 h. The third period was begun by replacing the PG infusion with saline, which was infused for a final 40-min period.

The effects of different doses of PG were measured in different groups of 8-13 subjects (designated the "group dose-response studies"), and 2 subjects had a complete dose-response examination (four or five studies at each of seven doses, designated the "individual dose-response studies"). In the group dose-response studies, the protocol was modified with the 0.9 and 1.5 $\mu\text{g}/\text{kg}$ per h PG infusions in that 0.5 $\mu\text{g}/\text{kg}$ PG was injected intravenously as a bolus at the end of the 1-h PG infusion. This is known to elicit a maximal LES contraction in otherwise unstimulated subjects (6, 12). The bolus was injected while the intravenous infusion of PG was still running.

²Peptavalon kindly supplied by Dr. John D. Stevens, Ayerst Laboratories, New York.

Using mean gastric fundal pressure as a zero reference, LES pressure was measured at 15-min intervals during the first and third periods and at 10-min intervals during the second (PG) period. At each interval LES was measured by two pull-throughs of the entire length of the LES. The highest pressure recorded at the end of inspiration was taken as the LES for each pull-through, and the results of the two pull-throughs (done within a 4-min period) were averaged. Fig. 1 shows the correlation of the first with the second pull-through when saline was infused throughout the three periods of study (placebo infusion in 13 subjects). While the two results often differed, overall there was good reproducibility, with a correlation coefficient of 0.87. Thus, the average of two pull-through pressures taken at 10- and 15-min intervals should be adequate to detect relative changes in LES induced by continuous infusion of PG.

In contrast to the pull-through method, the response of the sphincter to the bolus doses of PG was measured with the aperture of the catheter anchored in the LES.

RESULTS

Group dose-response studies. As shown in Figs. 2 and 3, gastric acid secretion was not stimulated by the 0.004 $\mu\text{g}/\text{kg}$ per h dose but was significantly increased by infusion of 0.025 $\mu\text{g}/\text{kg}$ per h and higher doses of PG. By contrast, continuous 1-h infusion of PG in doses ranging between 0.004 and 12 $\mu\text{g}/\text{kg}$ per h did not elevate average LES pressure significantly when the results

were analyzed by paired *t* test. LES pressure was reduced transiently from 26 to 22 mm Hg 10 min after starting the 2.1 $\mu\text{g}/\text{kg}$ per h dose ($P < 0.05$) and from 29 to 23 mm Hg 10 min after starting the 12 $\mu\text{g}/\text{kg}$ per h dose of PG ($P < 0.05$). As shown in Fig. 3, an intravenous bolus injection of PG (0.5 $\mu\text{g}/\text{kg}$) superimposed on the 0.9 and 1.5 $\mu\text{g}/\text{kg}$ per h PG infusion caused LES pressure to increase by approximately 20 mm Hg ($P < 0.001$).

Although PG by infusion failed to increase average LES pressure, examination of the results in individual subjects sometimes suggested that a given dose of PG might stimulate or inhibit LES pressure. Two examples are shown in Fig. 4. However, LES pressure sometimes changed during the course of a saline control infusion (Fig. 5), making it hazardous to interpret the results of a single study.

Individual dose-response studies. Additional studies were carried out in two normal subjects who agreed to have four measurements of LES pressure at PG infusion rates of 0.01, 0.025, 0.05, 0.1, 0.9, and 2.1 $\mu\text{g}/\text{kg}$ per h. LES pressure in subject A. C. (Fig. 6) was increased from 37 to a peak of 50 mm Hg with the 0.9 $\mu\text{g}/\text{kg}$ per h infusion rate ($P < 0.05$). Other doses of PG had no statistically significant effect. LES pressure in subject G. H. (Fig. 7) was increased from an average of 38 mm Hg with saline to a peak of 49 mm Hg with the 0.9 $\mu\text{g}/\text{kg}$ per h

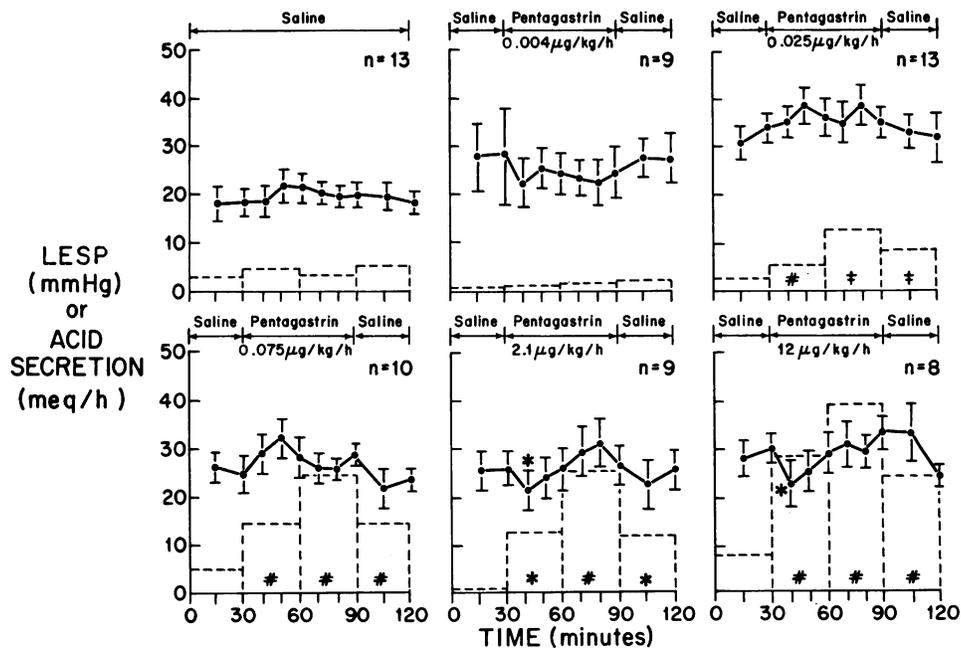


FIGURE 2 Group dose-response studies in 8-13 normal subjects. Mean LES pressure ± 1 SEM is indicated by points connected by lines at the top part of each graph, and mean acid secretion rate is shown at the bottom of each graph as dotted-line bar graphs. Statistical analysis for LES pressure was by paired *t* test, wherein the average of the two measurements during the saline control was compared with the results at each subsequent period. Statistics for gastric acid secretion compared basal secretion with that during each subsequent 30-min period. *P* values are denoted by the following symbols: * = $P < 0.05$; † = $P < 0.025$; ‡ = $P < 0.01$; and # = $P < 0.005$.

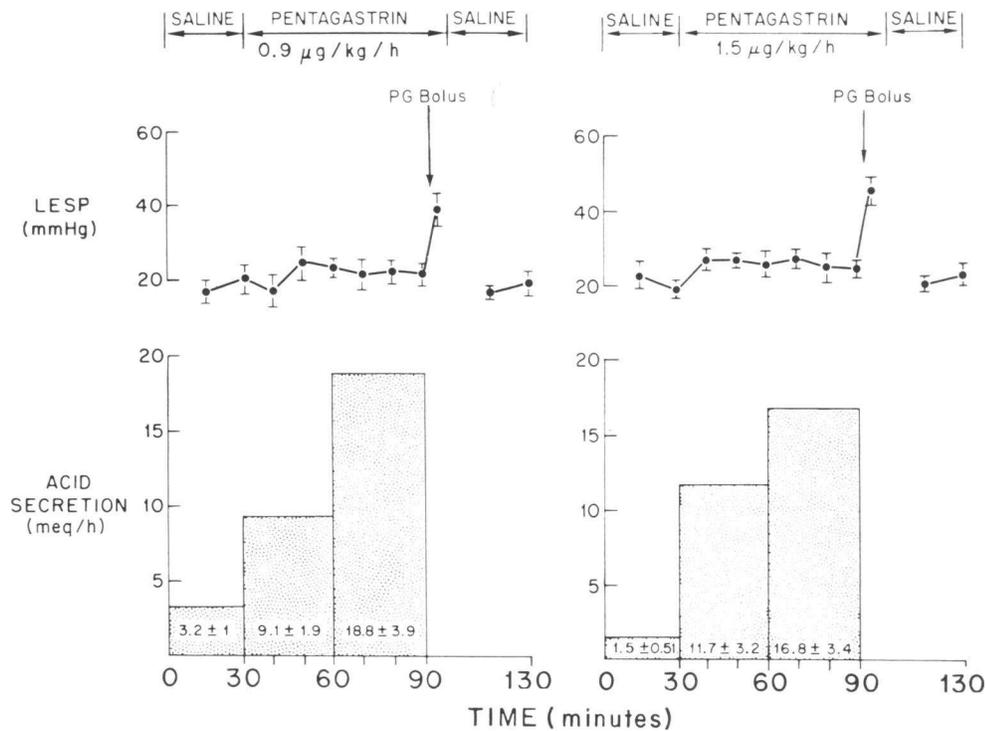


FIGURE 3 Group dose-response studies with PG infusion rates of 0.9 ($n=8$) and 1.5 ($n=12$) $\mu\text{g}/\text{kg}$ per h. These results are shown separately because a bolus of PG (0.5 $\mu\text{g}/\text{kg}$) was injected at 90 min while the PG infusion was continued. None of the LESP changes during the continuous infusion were statistically significant by paired t test. The rise in LESP after the bolus of PG was statistically significant.

PG infusion ($P < 0.005$) and was inhibited from an average 40 to 28 mm Hg with the 2.1 $\mu\text{g}/\text{kg}$ per h PG infusion. The inhibition was transient.

In both of these subjects the 0.9 $\mu\text{g}/\text{kg}$ per h dose of PG elicited secretion rates of gastric acid equal to that induced by a 12- $\mu\text{g}/\text{kg}$ per h PG infusion (19.9 meq/h for A. C. and 27.6 meq/h for G. H.).

In analyzing dose-response studies it is common practice to study a dose of drug that gives a half maximal response. Unfortunately, in neither subject did any of the PG infusion rates result in approximately half maximal secretion rates of gastric acid. A. C. and G. H. were, therefore, studied on five additional occasions with an infusion rate of PG calculated (on the basis of the data shown in Figs. 6 and 7) to give a half maximal acid secretory response during the second half-hour of the PG infusion. For A. C. this calculated D_{50} for acid secretion was 0.15 $\mu\text{g}/\text{kg}$ per h, and as shown in Fig. 8 this PG infusion rate resulted in approximately half maximal acid secretion and elevated LESP by a maximum of 8 mm Hg. For G. H. the calculated D_{50} for acid secretion was 0.35 $\mu\text{g}/\text{kg}$ per h and this infusion rate also resulted in approximately half maximal acid secretion; however, LESP was not increased (Fig. 8, right side).

Correlation of acid secretion and LESP. During the control saline infusion in subjects A. C. and G. H. (Figs. 6-8), acid secretion and LESP were measured on 29 separate test days. On each day LESP was measured four times during this 30-min period. In A. C. the average LESP varied from 16 to 68 mm Hg, and acid secretion varied from 0 to 5.6 meq/h. However, as shown in Fig. 9, there was no correlation between acid secretion rate and LESP. Results in G. H. were similar.

DISCUSSION

It is well established that intravenous bolus injections of PG cause a marked contraction of the LES. In contrast, we found that PG in doses ranging from 0.004 to 12 $\mu\text{g}/\text{kg}$ per h failed to elicit a rise in LESP when infused intravenously for 1 h in groups of 8 to 13 normal subjects. Not only did the sphincter fail to contract, but with high rates of PG infusion, LESP was transiently inhibited. It seems unlikely that our failure to find a rise in LESP with continuous infusion of PG could be due to release of inhibitory hormones from the duodenum such as secretin, since acid secreted by the stomach was removed continuously by aspiration. Furthermore, when a bolus of PG was superimposed on a continuous infusion of PG, the sphincter responded

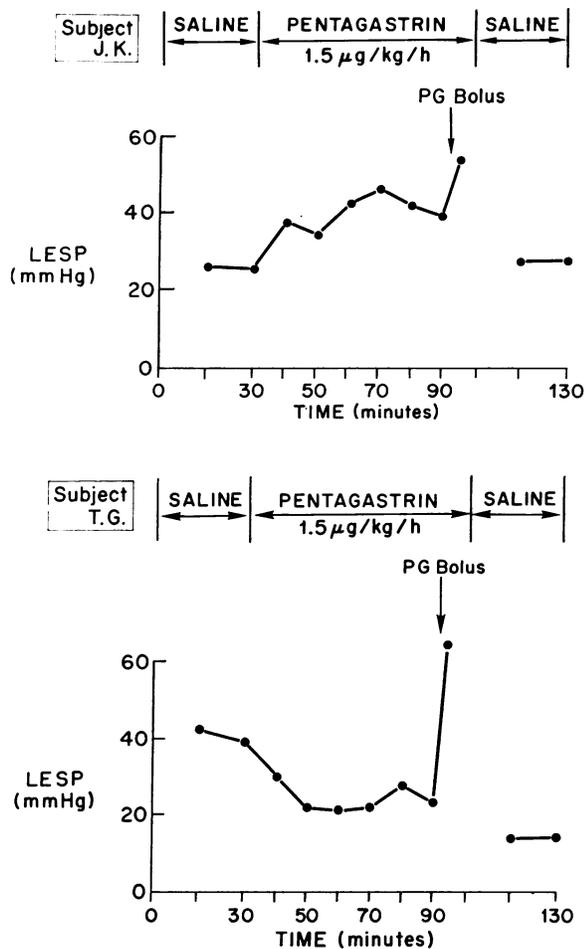


FIGURE 4 Results of single studies with $1.5 \mu\text{g}/\text{kg}$ per h PG infusion. In J. K. the PG infusion apparently elevated LESP, while in T. G. the PG infusion apparently reduced LESP.

with a 20-mm rise in pressure, indicating that it was still sensitive to the effects of a bolus injection of PG.

Although these average results with continuous PG infusions were negative insofar as sphincteric contraction was concerned, an examination of the results in individual subjects made us hesitant to conclude that PG by constant infusion has no stimulatory effect on LESP. Specifically, some subjects apparently developed a modest increase in LESP after PG infusion, but these were canceled by other subjects in whom PG seemed to depress LESP. However, speculation based on single studies was hazardous since sphincter pressure often changed in subjects infused with the saline control.

Two subjects were therefore selected at random to have four or five tests performed at each of seven PG infusion rates. In both subjects the infusion of $0.9 \mu\text{g}/\text{kg}$ per h PG elevated LESP by about 12 mm Hg. This

dose of PG also resulted in maximal stimulation of acid secretion. Both subjects were studied at a dose of PG calculated to give one-half maximal rate of acid secretion; in one this PG infusion rate caused the LESP to rise by 8 mm Hg, whereas in the other LESP was not effected. In neither subject did smaller doses of PG elevate LESP, even though acid secretion was increased. Thus, the parietal cells are more sensitive than the LES to the effects of PG infusion. In one of the subjects a dose of PG larger than that required for maximal acid secretion inhibited LESP transiently.

When LESP did increase with PG infusion, the onset of the rise was variable, sometimes occurring within the first 10 min of starting the infusion and sometimes not occurring until 30 or 40 min after the PG infusion was started. Once increased, LESP tended to remain elevated for the duration of the PG infusion. When PG was stopped, LESP returned to the base line within 15 min, even though gastric acid secretion remained much higher than the control value for at least 30 min afterwards.

We conclude from these individual dose-response studies that the LES response to PG by infusion is biphasic. First, within a narrow dose range PG by infusion causes the LES to contract. Second, at higher PG infusion rates the LESP is no longer increased, and at least in some subjects it is transiently inhibited. Most likely, the dose that will elicit a contraction or relaxation of the LES varies in different subjects, and this is probably the reason why average results in different groups of subjects failed to reveal any evidence of sphincteric contraction in response to continuous infusion of a wide range of doses; i.e., a given dose of PG might cause contraction in some subjects and relaxation in others, so that average sphincter pressure would not change.

The rise in LESP after continuous infusion of PG was much less than expected on the basis of studies in

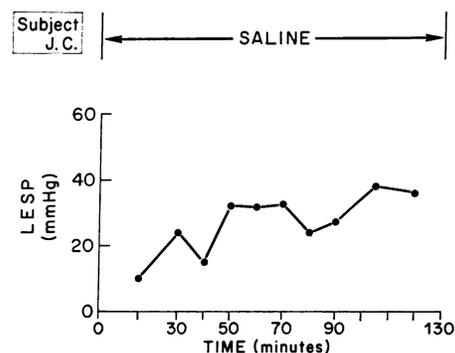


FIGURE 5 Results of a single study with saline infused throughout the experiment. The fluctuation in LESP makes it impossible to interpret the effect of drugs or hormones in a single experiment.

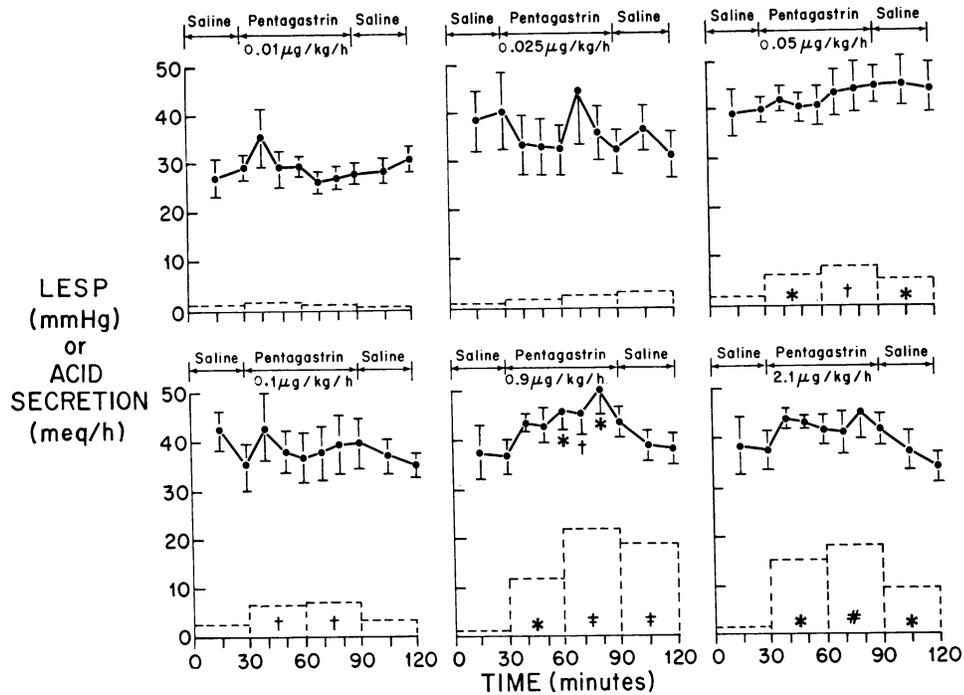


FIGURE 6 Individual dose-response study in subject A. C. Four studies were done with each of six PG infusion rates. See Fig. 2 for meaning of symbols.

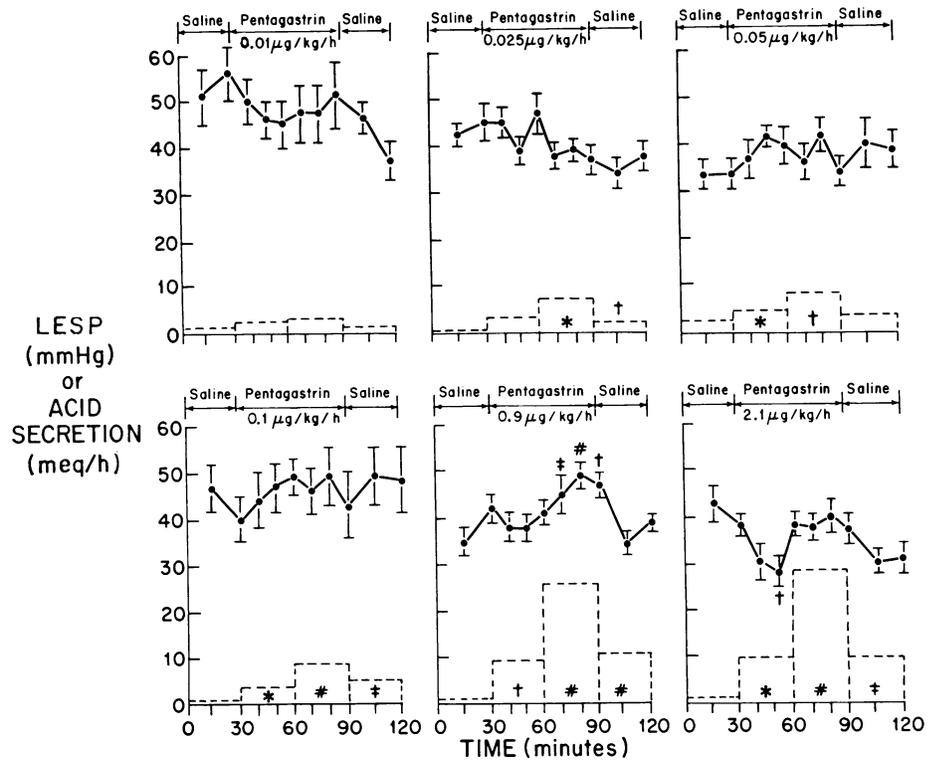


FIGURE 7 Individual dose-response study in subject G. M. Four studies were done with each of six PG infusion rates. See Fig. 2 for meaning of symbols.

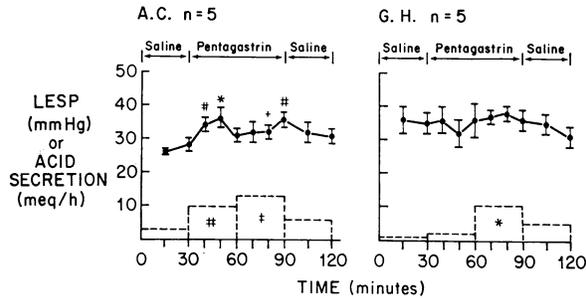


FIGURE 8 Effect of continuous infusion of PG at a dose calculated to stimulate acid secretion to one-half maximal rate during the second half-hour of the PG infusion. For subject A. C. this dose was $0.15 \mu\text{g}/\text{kg}$ per h and for subject G. H. this dose was $0.35 \mu\text{g}/\text{kg}$ per h. Five studies were done in each subject. See Fig. 2 for meaning of symbols for statistical significance.

which PG has been injected intravenously as a bolus. For example, most workers report an LESP rise of about 40 mm Hg after a bolus of $0.5 \mu\text{g}/\text{kg}$ PG (5, 6, 12), whereas the highest increase in pressure we could document after PG infusion was about 12 mm Hg. However, even our highest PG infusion rates probably do not result in steady blood or tissue concentration of PG comparable to those reached transiently after a bolus injection of $0.5 \mu\text{g}/\text{kg}$ PG. The reason why bolus injections of PG elicit a stronger contraction of the LES than is attained by constant PG infusion might therefore be because tissue concentrations are higher with the bolus. Alternatively, or in addition, continuous infusion of PG may cause the sphincter to become partially refractory to the stimulatory effect of PG (13, 14).

Because of the suggestion that basal LESP is determined by serum gastrin concentration (3, 5, 9) and that LESP gives an accurate assessment of serum gastrin activity (7, 10), it was of interest to correlate

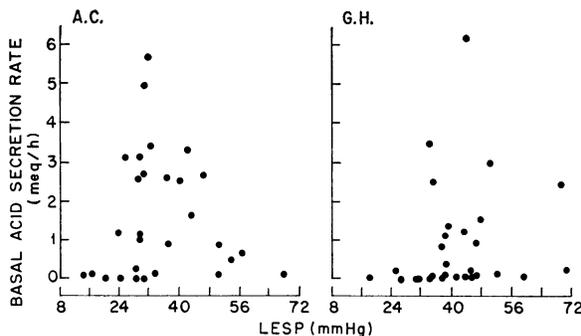


FIGURE 9 Correlation of basal acid secretion and basal LESP in subjects A. C. and G. H. Measurements were made on 29 separate days during the infusion of saline. During the 30-min test period LESP was measured four times by pull-through and the results in this figure are the mean of these four measurements.

basal LESP and basal acid secretion in our two subjects who were studied repeatedly. The basal LESP in these subjects was highly variable from day to day (from 16 to 71 mm Hg), but on a given day LESP was relatively stable. If this variation in day to day LESP was caused by different serum gastrin concentrations, gastric acid secretion should be high when the LESP is high, assuming that parietal cells are more sensitive than the LES to gastrin, as they are to PG. Basal LESP and gastric acid secretion were measured simultaneously on 29 separate test days in these two subjects, and there was no correlation between these two activities. This suggests that the wide day-to-day fluctuation in LESP is not due to changing concentration of gastrin in serum. Whether or not the fluctuations in basal acid secretion (from 0 to 6 meq/h) were due to differences in serum gastrin concentration is not known; however, this does not detract from our conclusion that changing LESP is not due to differences in serum gastrin concentration, provided our assumption is correct that parietal cells are more sensitive than LES muscle to changes in the concentration of serum gastrin(s) as they are to PG.

The present experiments confirm the previously known fact (15) that LESP is quite variable from day to day in the same normal subject, but they cast doubt on the hypothesis that serum gastrin concentration is the main determinant of LESP. Most likely there are multiple controls. Our data suggest that serum gastrin concentration could be one of these. For example, a rise in serum gastrin concentration might be the cause of the 4–8 mm Hg rise in LESP that is said to occur from 10 to 60 min after subjects ingest a high protein meal (7), provided the serum gastrin response to the meal was within the relatively narrow range required to stimulate contraction of the sphincter. It is very unlikely, however, that physiological changes in gastrin concentration could be responsible for the wide range of LESP that occur when a normal person is studied on different days (from 16 to 71 mm Hg in our two subjects); judging from our results, physiological changes in gastrin concentration could never cause more than an 8–12 mm Hg change in LESP. Therefore, we conclude that the role of gastrin as a physiological regulator of LESP is relatively minor.

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