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Research Article

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Studies on the Role of Cephalic-Vagal Stimulation in the Acid Secretory Response to Eating in Normal Human Subjects

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ABSTRACT These experiments were performed to determine the importance of cephalic-vagal stimulation in the acid secretory response to eating in normal human subjects. Cephalic stimulation was induced by a modified sham feeding (MSF) technique, during which subjects chewed and expectorated appetizing food. The response to MSF was compared with that to gastric distention with 600 ml NaCl, glucose, or food. In addition, we measured the extent to which cephalic stimulation augments acid secretion that has been stimulated simultaneously by these other mechanisms.

Our conclusions are as follows: (a) cephalic stimulation accounts for approximately one-third of the acid secreted when all mechanisms act simultaneously (food-distention plus MSF); (b) within the limits imposed by the maximal secretory capacity, the response to MSF is approximately the same, regardless of whether acid secretion is otherwise unstimulated or is stimulated simultaneously by gastric distention with NaCl, glucose, or food; and (c) gastric distention prolongs the response to cephalic stimulation.

INTRODUCTION

Eating food is believed to stimulate gastric acid secretion by three major physiological mechanisms: (a) cephalic-vagal stimulation secondary to anticipating, seeing, smelling, tasting, chewing, and swallowing food; (b) gastric distention which stimulates cholinergic reflexes in the body and fundus of the stomach

(1, 2); and (c) chemical reactions of food and digestive products with gastrointestinal mucosa, causing the release of stimulants of acid secretion such as gastrin (3, 4). It has also been suggested that amino acids and peptides may react directly with parietal cells to elicit acid secretion (5).

In humans, eating a steak meal stimulates acid secretion which, at its maximum, is approximately equal to the peak acid secretory response to a maximal dose of histamine (6). The relative importance of the three major physiologic mechanisms at various times during and after a meal has not been established, nor is it known to what extent cephalic stimulation augments acid secretion that has been stimulated by gastric distention or by food in the stomach.

There were two major purposes for the present experiments: first, to determine the relative secretory potency of cephalic-vagal stimulation, gastric distention with NaCl, and gastric distention with food; and second, to measure the extent cephalic-vagal stimulation augments acid secretion that has been stimulated simultaneously by gastric distention with NaCl, glucose, or food or by an intravenous infusion of pentagastrin. The effect of cephalic-vagal stimulation was assessed by measuring acid secretion in response to modified sham feeding (MSF)¹ (7).

METHODS

Subjects. Nine normal human subjects were studied with each stimulus (except that only five were studied with pentagastrin). Their mean age was 30 ± 2 yr (SEM) (range, 23–45 yr). Six were men and three were women. Basal

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¹Abbreviations used in this paper: MSF, modified sham feeding; PEG, polyethylene glycol.

and peak acid secretory responses to 0.04 mg/kg subcutaneous histamine acid phosphate were 3.2 ± 1.6 and 32.7 ± 4.6 meq/h (mean \pm SEM), respectively. Each subject was studied on separate test days after a 10-h fast, and the experiments were performed in random order (except for the penta-gastrin studies, which were performed after the other experiments were completed). The study was approved by a Human Research Review Committee and informed consent was obtained from each subject.

Gastric aspiration studies. Gastric contents were aspirated through a 16-Fr Salem sump tube (Sherwood Medical Industries, Inc., St. Louis, Mo.). The tip of the tube was placed in the gastric antrum under fluoroscopic control, and suction was applied for 48 out of every 60 s by a Stedman suction pump (American Cystoscope Makers Inc., Stamford, Conn.). Each sample of gastric juice was collected for 15 min, the volume was measured, and hydrogen ion concentration was determined by the method of Moore and Scarlata (8).

In vivo intragastric titration studies. Acid secretion in response to NaCl, glucose, or homogenized food infused into the stomach was measured by in vivo intragastric titration (6). Samples of gastric contents were obtained every 2–3 min through an Andersen tube (H. W. Andersen Products, Inc., Oyster Bay, N. Y.). pH was measured and the sample was returned to the stomach. Sodium bicarbonate (0.3 N) was infused through a small polyvinyl tube at the rate required to maintain pH at 5.0. The number of milliequivalents of bicarbonate required to prevent a fall of gastric pH below 5.0 is equal to the number of milliequivalents of acid secreted.

Modified sham feeding (MSF). During a 30-min period, the subjects chewed and expectorated an appetizing meal consisting of 227 g sirloin steak, 142 g french-fried potatoes, and 300 ml water. All meals were cooked in a separate building so that the subjects could not see or smell food until time for sham feeding. Subjects were trained in preliminary studies not to swallow food. During all experiments gastric aspirates were carefully examined for swallowed food, and none was found. As a further check, polyethylene glycol (PEG) was added to the 300-ml water part of the sham meal. Gastric samples were analyzed for PEG (9), and none was found.

Test meals. Three liquid test meals were given alone and in combination with MSF. Their composition was as follows: NaCl, 2.64 g NaCl; glucose, 14.6 g glucose; and homogenized food, 142 g ground lean cooked sirloin steak, 28 g bread, and 5 g butter. The meals were diluted with water to a final volume of 600 ml, and pH was adjusted to 5.0 by addition of sodium bicarbonate or hydrochloric acid. The osmolality of each meal was 138 mosmol/kg. Meals were infused over a 5-min period into the stomach through the Andersen tube.

Pentagastrin studies. On separate test days, either penta-gastrin (Peptavlon, Ayerst Laboratories, New York), 6.0 μ gm/kg per h or 0.15 M NaCl was infused intravenously at a constant rate (Harvard infusion pump, Harvard Apparatus Co., Inc., Millis, Mass.) for 150 min in five normal subjects. Gastric acid secretion was measured by aspiration. A steady state of acid secretion was achieved by the end of the first 30-min period. The effect of pentagastrin was assessed from 30 to 90 min. From 90 to 120 min MSF was superimposed on the continuing intravenous NaCl or pentagastrin infusion. Measurement of acid secretion was continued for two 30-min periods after the onset of MSF. The order of the experiments was randomized.

Serum gastrin. Venous blood was collected through an indwelling catheter (small vein infusion set, Pharmaseal Laboratories, Glendale, Calif.) which was kept open by a slow

saline infusion. Blood samples were obtained at 30-min intervals during the 90-min control period and at 15, 30, 45, 60, 90, and 120 min after infusion of the meals and (or) MSF. The blood was allowed to clot and serum was obtained by centrifugation and stored at -20°C until assayed.

Serum gastrin concentrations were measured by radioimmunoassay (10). All samples were tested in duplicate in the same assay. Antibody 1296, rabbit antigastrin prepared by immunization with gastrin conjugated to bovine serum albumin, was used at a final dilution of 1:300,000. With this antiserum, human heptadecapeptide gastrins (HG-17-I and HG-17-II) and human big gastrins (HG-34-I and HG-34-II) are measured on a nearly equimolar basis, big gastrins being approximately two-thirds as potent as heptadecapeptides. Cross reactivity with porcine cholecystokinin is less than 5% (11). Results are expressed in picograms per milliliter with natural human G-17-I used as standard.

Statistical analysis. Statistical significance of differences between mean values was determined with Student's *t* test for paired values. All differences with $P < 0.05$ are indicated in Figures and Tables.

RESULTS

Effect of MSF. Acid secretion rate in the basal state (90 min) and during and after 30 min of MSF is shown in Fig. 1 (left). As a control for MSF, the subjects chewed a piece of plastic tubing for 30 min. Gastric contents were collected by aspiration, and each 15-min sample was analyzed.

Acid secretion was stable during the 90-min basal period and did not change significantly during and after chewing plastic tubing. On the other hand, acid secretion increased from a basal level of 0.8 meq/15 min to 5.6 meq/15 min during the second 15-min period of MSF ($P < 0.05$). (For comparison, the peak acid output after histamine in these subjects was 8.2 meq/15 min). During the next 45 min, acid secretion decreased so that by 75 min (45 min after MSF ended) acid secretion had returned to near basal levels.

The reproducibility of MSF is shown in Fig. 2 in five subjects who had two studies approximately 6 mo apart. The correlation between the MSF response (acid secretion above the basal level) during the first and second studies was excellent with a correlation coefficient of 0.94 ($P < 0.01$).

As shown in Fig. 1 (right), serum gastrin concentration was not changed by aspiration of acid during the basal period nor by chewing plastic tubing. There was a slight increase in mean serum gastrin concentration during and after MSF, but the increase at each time period was not statistically significant ($P > 0.10$) when compared with basal levels or with levels after chewing plastic tubing.

Effect of gastric distention with NaCl or food. Basal acid secretion was measured by aspiration, and acid secretion after distention with NaCl or food was measured by in vivo intragastric titration. The results are shown in Fig. 3 (left). Acid secretion increased

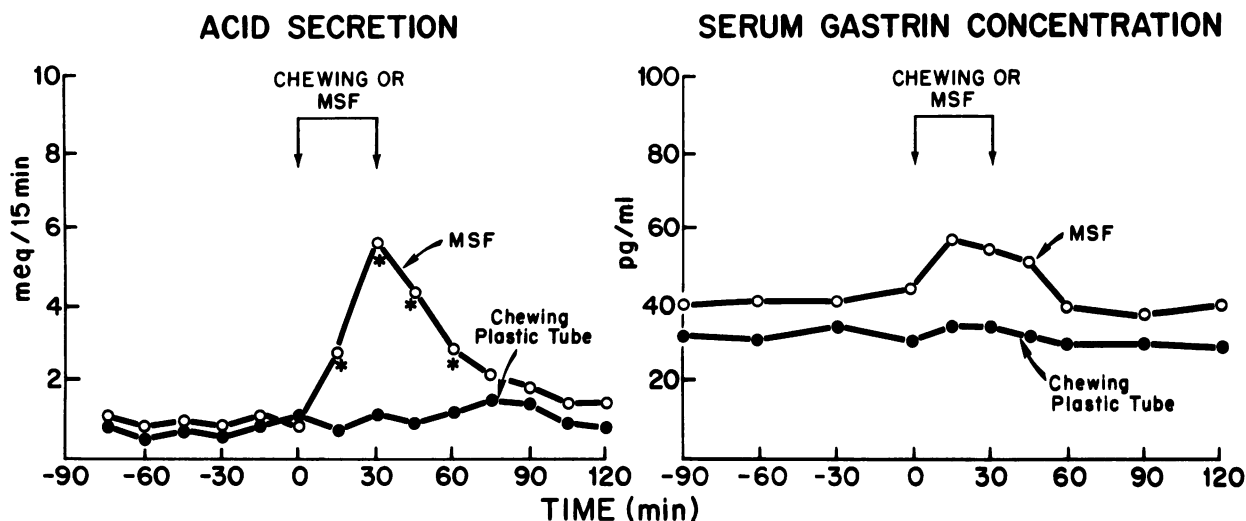


FIGURE 1 Acid secretion and serum gastrin concentration in nine normal subjects in the basal state and during and after 30 min of chewing a plastic tube or MSF. Acid secretion was measured by aspiration. Statistically significant differences ($P < 0.05$) by paired t test between the responses to MSF and chewing a plastic tube are shown by (*).

from a basal level of 0.8 to 2.8 meq/15 min during the first 15-min period after gastric distention with NaCl ($P < 0.05$); secretion remained near this level for the remainder of the experiment.

In contrast to distention with NaCl, distention with food did not cause an increase in acid secretion during the first 15-min period. However, during subsequent periods, acid secretion was higher with food than with NaCl and reached a peak of 6.8 meq/15 min at 60 min ($P < 0.05$). (For comparison the peak acid output to histamine was 8.2 meq/15 min).

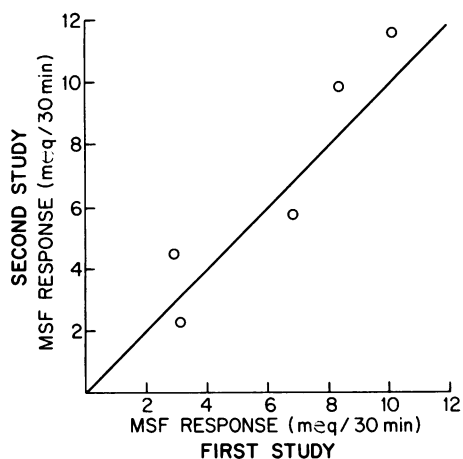


FIGURE 2 Reproducibility of MSF in five normal subjects. The MSF response (acid secretion above basal level) is shown for the 0–30-min time period on 2 separate test days (approximately 6 mo apart). The line represents perfect identity and not the regression line of the experimental observations. Correlation coefficient (r) for these observations is 0.94 ($P < 0.01$).

Distention with NaCl did not cause an increase in serum gastrin concentration over basal levels (Fig. 3, right). Distention with food, on the other hand, caused a rise in serum gastrin concentration from approximately 30 to 96 pg/ml. Serum gastrin concentration at each time period was significantly higher than basal values and also higher than those after NaCl (Fig. 3, right).

Relative potency of MSF and gastric distention with NaCl, glucose, or food. Acid secretory response (acid secretion above basal or control level) to each stimulus is shown in Table I. During the first 30-min period, the MSF response was the most potent. The response to gastric distention with NaCl was present during the first 30-min period and remained near the same level during subsequent periods. During the first period, the response to glucose distention was approximately the same as with NaCl, remained relatively steady during the second period, and then decreased during the last two periods. The food-distention response, on the other hand, was less than that with NaCl or glucose during the first period but during the latter periods was higher than any of the other responses. Peak acid secretory responses expressed as a percentage of the peak acid response to histamine (14.7 meq/30 min, basal acid secretion subtracted), were as follows: MSF, 45%; NaCl distention, 24%; glucose distention, 30%; and food distention, 65%.

Effect of MSF superimposed on NaCl, glucose, and food-distention stimuli. Each subject was studied with and without MSF under four conditions: gastric aspiration (stomach empty) (Fig. 1) and gastric distention with NaCl, glucose, or food (Fig. 4 and Table II). MSF had approximately the same effect on acid

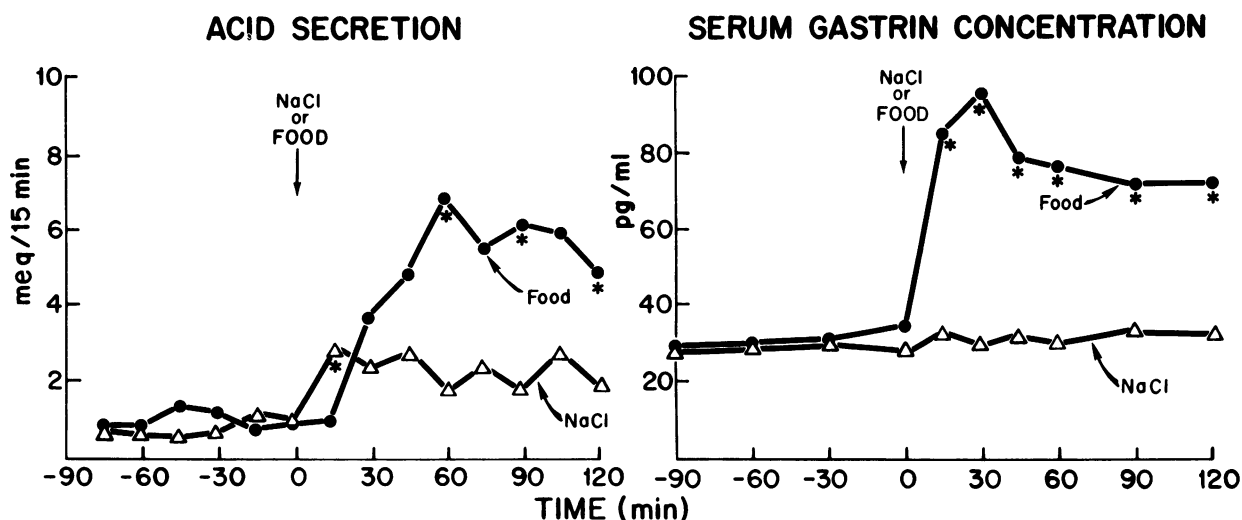


FIGURE 3 Acid secretion and serum gastrin concentration in nine normal subjects in the basal state and after 600 ml NaCl or homogenized food was infused into the stomach. Acid secretion was measured by in vivo intragastric titration. Statistically significant differences ($P < 0.05$) by paired t test between food and NaCl responses are shown by (*).

TABLE I
Relative Potency of MSF and Gastric Distention
with NaCl, Glucose, or Food*

| | Acid secretory response | | | |
|--------------------|-------------------------|-----------|-----------|------------|
| | 0-30 min | 30-60 min | 60-90 min | 90-120 min |
| | meq/30 min † | | | |
| MSF | 6.6±1.4 | 5.4±1.1 | 2.2±0.9 | 1.1±0.9 |
| Gastric distention | | | | |
| NaCl | 3.5±0.7 | 2.8±1.2 | 2.6±0.6 | 3.0±0.9 |
| Glucose | 3.6±1.1 | 4.4±1.1 | 2.0±1.0 | 1.0±0.6 |
| Food | 2.6±1.7 | 9.5±2.0 | 9.6±2.6 | 8.7±1.6 |

* Response to MSF or gastric distention with NaCl, glucose, or food is defined as acid secretion with each stimulus minus basal secretion. Basal acid secretion was measured before each experiment. Mean basal acid secretion before MSF was 1.7 ± 0.9 ; NaCl distention, 1.6 ± 0.8 ; glucose distention, 1.7 ± 0.7 ; and food distention 2.3 ± 1.0 meq/30 min.

† Mean \pm SEM.

secretion from 0-30 and 30-60 min whether the stomach was empty or distended by NaCl, glucose, or food. On the other hand, the response to MSF was of longer duration when the stomach was distended than when it was empty (compare Fig. 1, left, with Fig. 4, top panel). Peak acid secretion after MSF plus gastric distention with food was 9.7 meq/15 min (Fig. 4). This exceeded the peak acid output to histamine (8.2 meq/15 min) although the difference was not statistically significant.

The contribution of MSF (net effect of MSF) to acid

secretion when all mechanisms were acting simultaneously (food-distention plus MSF) is shown in Table III. MSF accounted for 30-51% of the acid secreted in response to these combined stimuli. When the total 2-h period is considered, MSF contributed 36%.²

Under each experimental condition, the mean serum gastrin concentration was higher with MSF at all blood sampling intervals (Fig. 1, right and Fig. 4, bottom panel), and, at several intervals the differences were statistically significant.

Effect of MSF on pentagastrin stimulated acid secretion. The effect of MSF on acid secretion stimulated by a maximal dose of pentagastrin (12, 13) is shown in Table IV. MSF did not augment maximally stimulated acid secretion.

DISCUSSION

Cephalic-vagal stimulation of gastric acid secretion is thought to be mediated by direct cholinergic innervation of parietal cells and by cholinergic stimulation of gastrin release from the antrum and (or) duodenum (3). In dogs sham feeding causes a 100-130 pg/ml increase in serum gastrin concentration, provided acid

² The net contribution of MSF to the total (all mechanisms acting simultaneously) 2-h response (60.7 meq) is also 36% when the MSF response superimposed on saline distention (21.9 meq) is used rather than the MSF response superimposed on food distention (as in Table III). Thus, the contribution of MSF to the overall response is the same, whether or not the MSF component is assessed with food in the stomach.

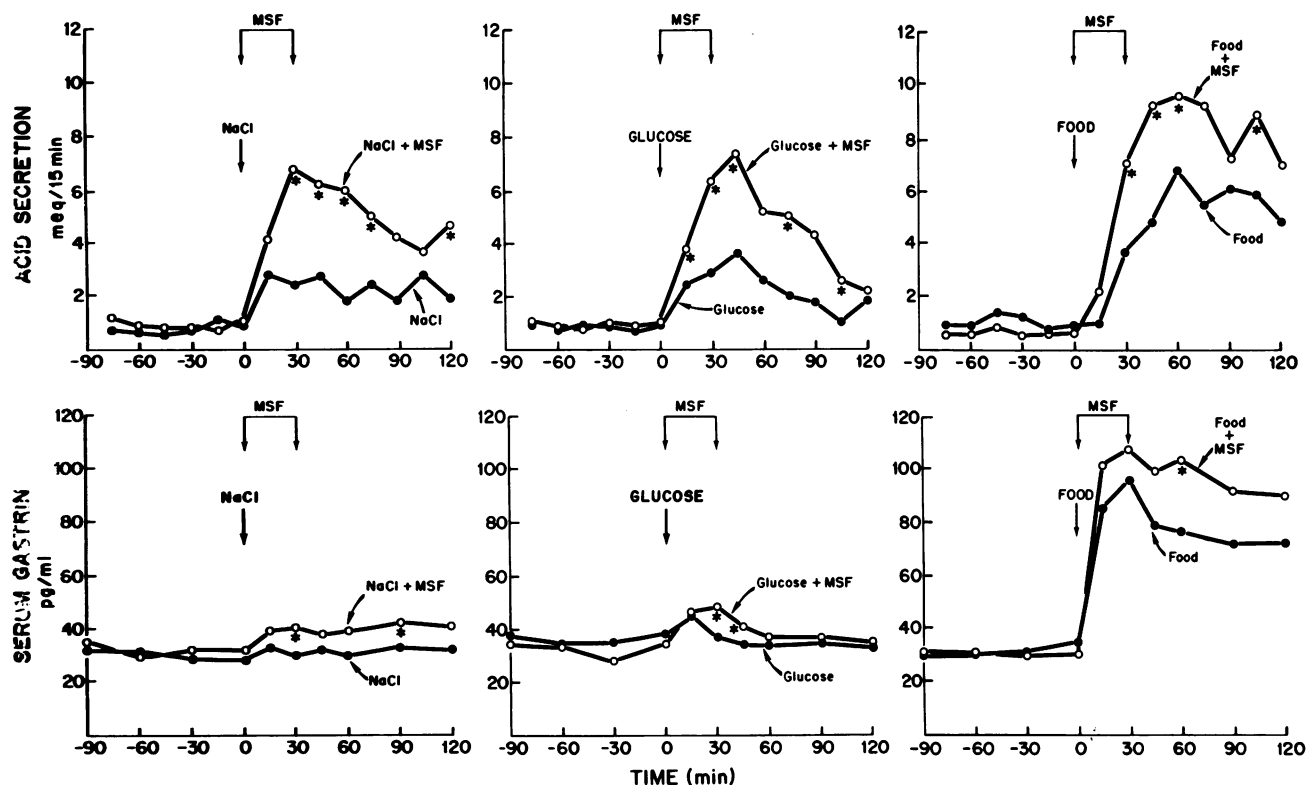


FIGURE 4 Acid secretion (top panel) and serum gastrin concentration (bottom panel) in nine normal subjects in the basal state and after 600 ml NaCl, glucose, or homogenized food was infused into the stomach. Each experiment was performed with and without MSF. Statistically significant differences ($P < 0.05$) by paired t test between each stimulus alone and with MSF is shown by (*).

TABLE II
Acid Secretory Responses to MSF under Four Experimental Conditions

| Background stimulus | Acid secretory response to MSF | | | |
|---------------------|--------------------------------|-----------|-----------|------------|
| | 0-30 min | 30-60 min | 60-90 min | 90-120 min |
| | <i>meq/30 min*</i> | | | |
| None‡ | 6.6±1.4 | 5.4±1.1 | 2.2±0.9 | 1.1±0.9 |
| NaCl distention§ | 5.8±1.4 | 7.6±2.2 | 5.0±2.3 | 3.5±1.4 |
| Glucose distention§ | 4.6±1.2 | 6.2±2.4 | 5.4±2.1 | 2.0±0.6 |
| Food distention§ | 4.7±1.0 | 7.2±2.3 | 4.8±2.3 | 5.0±3.0 |

* Mean±SEM.

‡ Acid secretion with MSF alone (gastric aspiration, stomach empty) minus basal acid secretion. Basal acid secretion was 1.7 ± 0.9 meq/30 min.

§ Mean acid secretory response to MSF was calculated by subtracting the observed rate of acid secretion with the background stimulus alone from the observed rate of acid secretion with the background stimulus plus MSF in each subject.

secreted in the fundus is diverted from the antrum (thus preventing feedback inhibition of gastrin release) (14, 15). The rise is less marked when normal gastric continuity allows acid to reach the antrum. Previous studies in normal humans have not shown a statistically significant increase in serum gastrin concentration with MSF (7, 16). However, in these studies acid secretion was measured by standard aspiration techniques which probably allow some acid to bathe the antral and duodenal mucosa. When we measured acid secretion by aspiration (Fig. 1), we also found that sham feeding did not cause a statistically significant increase in serum gastrin concentration. However, when the stomach was distended and intragastric pH maintained at 5.0 (Fig. 4), there was a 10-20 pg/ml rise in serum gastrin concentration with MSF, and this rise was statistically significant at several sampling intervals. We conclude that MSF increases serum gastrin concentration when the stomach is distended and gastric pH is 5.0, although the rise is small compared to the gastrin response to sham feeding in dogs. The extent to which a 10-20 pg/ml rise in serum gastrin concentration contributes to the acid secretory response to MSF is

TABLE III
Contribution of MSF to Acid Secretion* When All Mechanisms Are Acting Simultaneously

| | Acid secretion | | | | |
|--|---------------------|-----------|-----------|------------|-----------|
| | 0-30 min | 30-60 min | 60-90 min | 90-120 min | 0-120 min |
| | <i>meq/30 min</i> † | | | | |
| Food distention | 4.6±1.7 | 11.6±2.4 | 11.7±2.6 | 10.8±1.8 | 38.7±7.7 |
| Food distention plus MSF | 9.3±1.7 | 18.8±3.0 | 16.6±2.6 | 16.0±2.3 | 60.7±9.0 |
| Net effect of MSF: | | | | | |
| <i>meq/30 min</i> § | 4.7±1.0 | 7.2±2.3 | 4.8±2.3 | 5.0±3.0 | 21.7±3.0 |
| Percent of food distention plus MSF, % | 51 | 38 | 30 | 31 | 36 |

* In contrast to data shown in Table 1 basal acid secretion has not been subtracted from acid secretion shown in this Table.

† Mean±SEM.

§ Calculated by subtracting acid secretion with food distention from acid secretion with food distention plus MSF in each subject.

TABLE IV
Effect of MSF on Unstimulated and Maximally Stimulated Acid Secretion in Five Normal Subjects

| Intravenous infusate | Time, min | | | |
|----------------------|---------------------|----------|----------------------|----------|
| | Before MSF | | During and after MSF | |
| | 30-60 | 60-90 | 90-120 | 120-150 |
| | <i>meq/30 min</i> * | | | |
| 0.15 M NaCl | 1.3±0.8 | 1.8±1.2 | 8.3±2.5 | 7.3±2.4 |
| Penta-gastrin † | 25.9±3.9 | 24.8±4.2 | 26.6±4.1 | 25.2±4.2 |

* Mean±SEM.

† 6.0 µgm/kg per h.

not clear. Based on studies in which exogenous gastrin has been infused, and acid secretion compared with serum gastrin concentration (17), it seems likely that rises in gastrin concentration of this magnitude can cause some but not all of the acid secretory response to sham feeding in humans.

The contribution of the cephalic phase of acid secretion in the overall acid secretory response to eating has not been investigated previously. To evaluate the relative importance of cephalic-vagal stimulation, gastric distention and the chemical effects of food, we studied each of these stimulants in nine normal subjects. The peak secretory responses, expressed as a percentage of the peak histamine response, were 45, 24, and 65% for MSF, gastric distention with NaCl, and gastric distention with food, respectively. Thus, the peak MSF response was intermediate between the responses to NaCl and food distention and none of the responses, acting alone, caused maximum acid secretion. Although this is the first time that responses to these three stimulants have been measured and com-

pared in the same normal subjects, the response to each stimulant is similar to that found in previous studies (7, 16, 18-20).

Not only were the peak secretory responses to the three stimulants different but also the patterns of acid secretion. The response to MSF was prompt but transient; soon after MSF was discontinued, acid secretion decreased rapidly and reached near basal rates within 45 min. Gastric distention with NaCl initiated a prompt (but modest) secretory response that persisted at approximately the same level throughout the 2-h experiment. In contrast, the response to food was delayed for 15 min, but then increased rapidly, reaching a peak at 60 min. The 15-min delay in acid secretion presumably occurred because food released inhibitors which counteracted the acid stimulatory effects of distention and the increased serum gastrin concentration noted at 15 min (Fig. 3).

Since, under physiologic conditions, cephalic stimulation occurs in concert with other stimuli, we also measured the response to MSF when the stomach was distended. MSF caused approximately the same peak increment in acid secretion when the stomach was distended with 600 ml NaCl as it did when the stomach was empty, but distention prolonged the secretory response to MSF. Even at the end of the 2-h experiment, acid secretion was still significantly higher than the control rate noted with NaCl distention alone. This suggests that when the stomach has been primed by distention, the cephalic phase of acid secretion persists for at least 90 min after eating has ceased.

The next aspect of these studies was designed to determine the extent to which MSF augments acid secretion stimulated simultaneously by gastric distention with food. The net increment in acid secretion in response to MSF was the same whether MSF was the only stimulus or whether it was superimposed on a food distention stimulus. Thus, the effect of MSF is

numerically additive with the effect of food distention. It might be argued that numerically additive responses suggest potentiation between stimuli. For example, for responses that obey Michaelis-Menton kinetics, the expected response to two nonpotentiating stimuli given simultaneously is less than (rather than numerically equal to) the sum of the responses to the two stimuli given separately. Unfortunately, it is not known if the parietal cell response to combined nonpotentiating stimuli would obey the Michaelis-Menton formula; therefore, our data does not prove or disprove potentiation between food-distention and cephalic-vagal stimulation of acid secretion.

In conclusion, within the limits imposed by the maximal secretory capacity, the peak response to MSF is approximately the same, regardless of the background rate of acid secretion or the background stimulus (NaCl, glucose, or food). When the stomach is distended, as would occur when a meal is ingested, the secretory response to MSF is prolonged and continues for at least 90 min after sham feeding has been discontinued. Since cephalic-vagal stimulation accounts for approximately one-third of the acid secreted when all mechanisms act simultaneously (MSF plus food-distention), increased vagal activity secondary to cephalic influences is an important mediator of acid secretion during and after a meal is eaten.

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