

# Fat inhibition of gastric acid secretion in duodenal ulcer patients before and after proximal gastric vagotomy

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**SUMMARY** In seven duodenal ulcer patients the effect of intraduodenal infusion of 20 ml oleic acid on submaximal gastric acid secretion stimulated by a continuous pentagastrin infusion was evaluated before and after proximal gastric vagotomy. In the control tests 20 ml of saline was given. Before vagotomy, oleic acid evoked a significant inhibition of gastric acid secretion of 25% compared with the controls. This inhibition was abolished after proximal gastric vagotomy. The difference in inhibition before and after vagotomy was significant ( $P=0.01$ ). It is concluded that the vagus nerve in man plays a decisive role in duodenal fat inhibition of gastric acid secretion.

The observation by Ewald and Boas in 1886 that fat added to a test meal reduces gastric acid secretion and delays gastric emptying is probably the first description of the two inhibitive effects of fat—that is, the effects on motility and gastric acid secretion.<sup>1</sup> Since then extensive work has been carried out in order to clarify the mechanisms of fat inhibition. Considerable evidence has been gathered suggesting a fat-induced release of a hormone(s) from the intestine which inhibits gastric acid secretion in both dog and man.<sup>2-10</sup> Most studies are consistent with the concept that the vagal nerve does not play a significant role in fat inhibition of gastric acid secretion. However, an impairment of fat inhibition of gastric acid secretion in duodenal ulcer patients after truncal as well as highly selective vagotomy has been observed.<sup>9,11</sup>

The aim of the present study was to evaluate the effect of proximal gastric vagotomy (PGV) on the inhibition evoked by a small dose (20 ml) of intraduodenally administered oleic acid on pentagastrin-stimulated gastric acid secretion in duodenal ulcer patients. Graded intraduodenal administration of oleic acid in healthy subjects has revealed that 20 ml of oleic acid is the lowest dose that elicits maximal inhibition.<sup>12</sup>

## Methods

### PATIENTS

Seven patients, six men and one woman, aged

between 23 and 61 years of age (mean 43 years) were studied before and four to 15 weeks (mean seven weeks) after PGV for duodenal ulcer. All patients had a history of recurrent duodenal ulcerations and endoscopically verified ulcers. None of the patients had any signs or symptoms consistent with gastric outlet obstruction.

### EXPERIMENTAL PROCEDURE

An overnight fast preceded all tests. Each patient was, before oleic acid or control studies with normal saline, subjected to a three-dose pentagastrin (Peptavlon, ICI) regime. This was performed in order to find what dose of pentagastrin evoked a submaximal gastric acid response (>50% of the maximal). The three-dose pentagastrin test was repeated after PGV. Basal acid secretion was collected for one hour and pentagastrin then intravenously infused in three successive doses, 16.2, 90.8, and 198 µg/hour. Each dose was given for one hour. Peak acid output to pentagastrin was defined as the sum of the two highest consecutive 15 minute samples. Gastric secretion was collected in 15 minute samples by means of a double-lumen nasogastric suction tube (Salem tube drain, Ch 14). The tip of the tube was placed in the gastric antrum with the aid of fluoroscopy. A negative pressure of 100 cm water once a second was used for continuous collection of gastric contents. A thin polyethylene catheter was attached to the nasogastric suction tube and placed in the fundic region of the stomach. It was used for perfusion of the stomach with a

solution of distilled water containing the non-absorbable marker phenol red. Eight milligrams of phenol red was added to 1 litre of the perfusate. The perfusate was administered by continuous infusion of 220 ml/15 min period during the tests. The concentration of phenol red in each gastric sample was measured using a Beckman B spectrophotometer at a wavelength of 565 nm, after passing the sample through a 1.2  $\mu$  Millipore filter and alkalisation to pH 12. Extinction of the perfusate was always read simultaneously. Pyloric losses of gastric contents could then be estimated under the assumption that homogeneous mixing of the perfusate and the gastric secretion took place in the stomach.

#### GASTRIC ACID ANALYSIS

In each gastric sample volume and pH were determined. The concentration of H<sup>+</sup> was determined by an autotitrator (Radiometer, Copenhagen) against 0.1 mol/l sodium hydroxide to pH 7. After correction for pyloric losses the calculated gastric output was expressed in mmol/15 min.

#### EXPERIMENTS WITH INTRADUODENAL OLEIC ACID INFUSION

The nasogastric suction tube was placed as described and a duodenal tube fluoroscopically positioned to the proximity of the duodenojejunal flexure. Oleic acid or saline was administered through a separate channel ending at the tip of the tube. A Bilbao-Dotter torque cable was used to place the duodenal tube. Intermittent suction with a negative pressure of 50 cm H<sub>2</sub>O once a second was used for collection of the duodenal contents. Volume and pH were determined in each 15-min sample.

After collection of basal gastric secretions for one hour pentagastrin was administered intravenously over a three hour period in a submaximal dose according to the three-dose pentagastrin infusion. Before PGV the pentagastrin dose chosen as a submaximal stimulus for gastric secretion was 16.2  $\mu$ g/hour in all patients. After PGV the pentagastrin dose was the same in most patients but in two patients a pentagastrin dose of 90.8  $\mu$ g/hour was chosen.

After one hour of pentagastrin infusion, when a stable rate of gastric acid secretion has been reached, an intraduodenal infusion of 20 ml oleic acid or saline was given in a randomised order. Oleic acid or normal saline was administered over a three-minute period and the collection of gastric contents continued for two hours. In the 15 minute period after the administration of oleic acid or normal saline duodenal suction was applied only over the final three minutes in order to allow the oleic acid

to be propagated from the duodenum to the small intestine. Gastric juice and duodenal contents were continuously checked to ensure that a free flow was maintained.

The median acid secretion during the half hour preceding the intraduodenal administration before PGV amounted in the saline experiments to 84% (range 74–96) of the maximal response in the three-dose pentagastrin tests and to 87% (range 80–100) in the oleic acid experiments, and after PGV to 70% (range 39–100) in the control tests and to 71% (range 42–100) in the oleic acid experiments.

#### STATISTICAL EVALUATIONS

In the comparison between saline and oleic acid experiments Wilcoxon's matched-pairs signed-ranks test was used.<sup>13</sup> The Mann-Whitney U-test was used in the comparison of the inhibition induced by oleic acid before and after PGV. *P* values equal to or below 0.05 were regarded as significant.

#### EVALUATION OF THE COMPLETENESS OF PROXIMAL GASTRIC VAGOTOMY

The completeness of PGV was tested by determining the acid secretion stimulated by insulin and/or sham-feeding three to six weeks postoperatively. Insulin tests were carried out using 0.2 U insulin/kg body weight intravenously. Sham feeding was carried out according to the method of Stenquist *et al.*<sup>14,15</sup> Basal secretion was collected for one or one-and-a-half hours. After stimulation the secretion was determined over two or two-and-a-half hours. Basal acid output was defined as the output during the last 30 minutes preceding insulin or sham feeding. The peak acid response was defined as the peak 30 minute gastric acid output after insulin or sham feeding.

#### CALCULATIONS OF INHIBITION

The inhibition of gastric acid secretion evoked by intraduodenal oleic acid infusion was calculated in two ways:

##### *Overall inhibition*

This was defined as the inhibition of gastric acid secretion over the period 15 to 120 minutes after intraduodenal administration of oleic acid. Overall inhibition was expressed as a percentage after correction for the slight fading in the control experiments. The acid outputs in oleic acid and control experiments were normalised with regard to the respective output in the 30-minute period preceding the intraduodenal administration and the inhibition represents the difference between the control and oleic acid experiments.

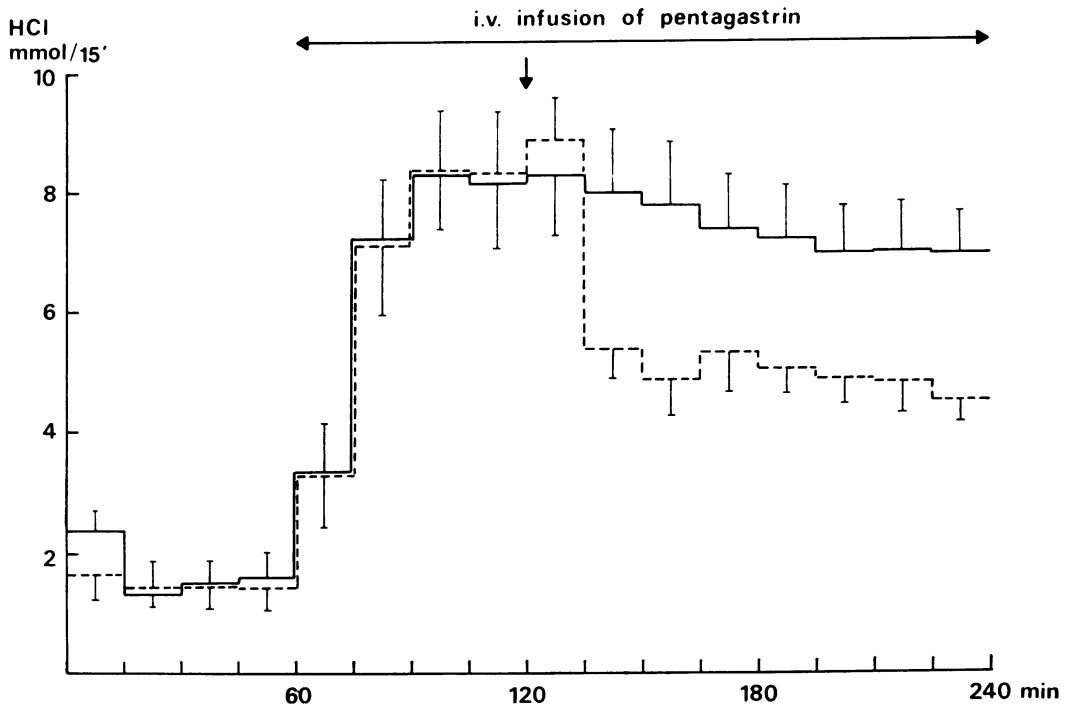


Fig. 1 Mean gastric acid output in mmol/15 min period  $\pm$  SEM after intraduodenal administration of 20 ml normal saline (solid line) or 20 ml oleic acid (broken line) on submaximal pentagastrin-stimulated gastric acid secretion in seven duodenal ulcer patients before proximal gastric vagotomy.  $\downarrow$  = intraduodenal administration.

### Maximal inhibition

This was defined as the highest percentage inhibition observed in any 15 minute period after fat administration comparing oleic acid and control experiments.

### Results

Before PGV the median overall inhibition was 25% (range -10-57) ( $p < 0.05$ ) (Fig. 1). Median maximal inhibition was 32% and observed in the

third 15 minute period after oleic acid infusion (Fig. 1). In all 15 minute periods after oleic acid administration except the first there was a significant inhibition of gastric acid secretion compared with controls ( $p \leq 0.05$ ). Median phenol red recovery in control and oleic acid experiments was 94% (Table 1). In two patients, EP and JOS, the pH in the duodenal samples was consistently low in the oleic acid tests, ranging between 1.2-1.6 and 1.4-1.6 respectively. In patient JOS the pH was also low in the control experiment, ranging from 1.4-1.6. In the

Table 1 Percentage inhibition of gastric acid secretion, median phenol red recovery and duodenal pH in the period 15 to 120 minutes after intraduodenal oleic acid infusion in patients before and after PGV

Subject	Before PGV					After PGV				
	% inhibition	Mean phenol red recovery		Duodenal pH		% inhibition	Mean phenol red recovery		Duodenal pH	
		Saline	Oleic acid	Saline	Oleic acid		Saline	Oleic acid	Saline	Oleic acid
PB	56.6	94	93	$\geq 6.9$	$\geq 6.5$	18.2	92	92	$\geq 7.6$	$\geq 6.8$
EH	33.0	94	97	$\geq 6.8$	$\geq 5.9$	25.3	91	100	$\geq 4.1$	$\geq 4.6$
EP	26.4	93	91	2.6-8.0	1.2-1.6	-1.3	91	94	2.1-5.7	1.5-2.0
EB	25.4	101	97	$\geq 4.0$	$\geq 6.3$	-19.0	92	100	$\geq 5.8$	$\geq 5.6$
SA	24.8	93	94	$\geq 7.6$	$\geq 7.5$	-10.4	97	95	$\geq 7.0$	$\geq 6.1$
SN	22.7	94	90	$\geq 8.1$	2.3-7.7	12.6	94	98	$\geq 7.7$	$\geq 6.7$
JOS	-10.1	89	93	1.4-1.6	1.4-1.6	4.3	83	94	2.0-2.8	1.2-2.5
Median	25	94	94			4	92	95		

Table 2 Gastric acid responses to intravenous insulin 0.2 U/kg bw (Ins) and/or to sham feeding (Sh) in seven duodenal ulcer patients after proximal gastric vagotomy

Subjects	BAO	PAO	Hollander
PB <sub>Sh</sub>	0.17	0.58	—
EH <sub>Ins</sub>	2.56	1.08	—
EP <sub>Ins</sub>	0.06	0.93	L+
EB <sub>Ins</sub>	0	0	—
EB <sub>Sh</sub>	0	0.09	—
SA <sub>Sh</sub>	0	0.10	—
SN <sub>Sh</sub>	0.14	0.63	—
JOS <sub>Ins</sub>	0	0.21	—
JOS <sub>Sh</sub>	0	0.23	—

BAO=basal acid output (mmol/30 min). PAO=peak acid output (mmol/30 min). Hollander: gastric acid concentration increase above 20 mmol/l. L + : Hollander positive in the second hour after insulin.

other patients, duodenal pH was above 5.6, except in one patient, SN, in whom the pH in the last two samples in the oleic acid experiments was 2.3 and 2.5 respectively (Table 1).

The data to evaluate the completeness of vagotomy are summarised in Table 2. One insulin test was late positive according to Hollander's criterion (patient EP). Pre- and postoperative fat inhibition in this patient was similar to that in the other patients. In two patients, EB and JOS, subjected to insulin as well as sham feeding tests, there was a good agreement between the two tests (Table 2).

After PGV the median overall inhibition was 4% (range -19-25) (Fig. 2). This inhibition was not significant compared with the controls. Median maximal inhibition was 11% and appeared in the second 15 minute period after oleic acid. Significant inhibition was observed only in the sixth and eighth 15 minute periods (P=0.05). There was,

however, a significant difference in inhibition between tests carried out before and after PGV (P=0.013). Median phenol red recovery in the control and the oleic acid experiments was 92 and 95% respectively (Table 1). After PGV duodenal pH was again found to be low in patients EP and JOS. Duodenal pH in the control experiments was 2.1-5.7 and 2.0-2.8 respectively. In the oleic acid experiments the corresponding figures were 1.5-2.0 (EP) and 1.2-2.5 (JOS) (Table 1).

The individual percentage inhibition, mean phenol red recovery, and duodenal pH are listed in Table 1. Three patients were postoperatively also tested with 40 ml oleic acid, which did not evoke any gastric acid inhibition (Fig. 3). In patient JOS, who consistently had low duodenal pH-values in all tests (Table 1), a postoperative test with 40 ml oleic acid and alkaline buffer perfusion of the stomach was also carried out with no detectable inhibition of gastric acid secretion.

Discussion

The role of the vagus nerve in the mechanism(s) by which fat inhibits gastric acid secretion in man is controversial. In gastrectomised Heidenhain pouch dogs the introduction of 100 ml corn oil in the intestine inhibits histamine-stimulated secretion to the same extent before and after truncal vagotomy.<sup>4</sup> After simultaneous vagotomy of the stomach and small intestine by truncal vagotomy in duodenal ulcer patients intraduodenal fat (20 ml of a commercial emulsion of ground nut oil) evokes a marked inhibition of pentagastrin-stimulated gastric acid secretion.<sup>8</sup> However, Johnston and Duthie<sup>7</sup> reported

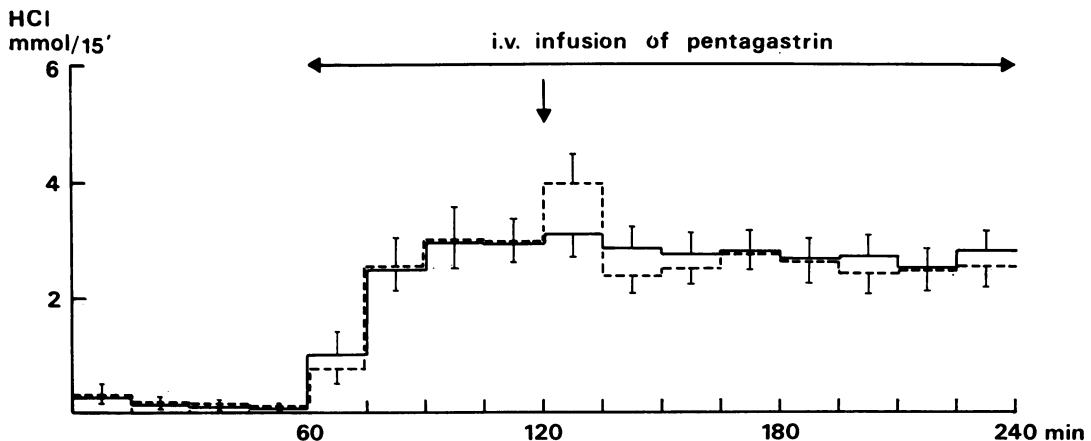


Fig. 2 Mean gastric acid output in mmol/15 min period ± SEM after intraduodenal administration of 20 ml normal saline (solid line) or 20 ml oleic acid (broken line) on submaximal pentagastrin-stimulated gastric acid secretion in seven duodenal ulcer patients after proximal gastric vagotomy. ↓ = intraduodenal administration.

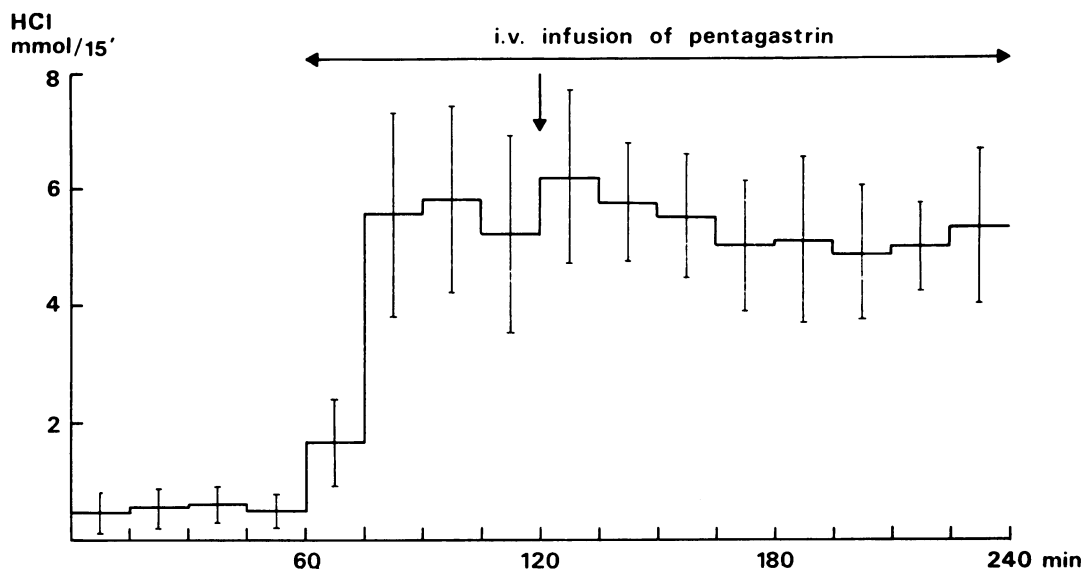


Fig. 3 Mean gastric acid output in mmol/15 min period  $\pm$  SEM after intraduodenal administration of 40 ml oleic acid on submaximal pentagastrin-stimulated secretion in three patients (JOS, SA, SN) after proximal gastric vagotomy.  $\downarrow$  = intraduodenal administration.

that an intraduodenal infusion of 60 ml pure olive oil and an equal amount of the subject's own duodenal aspirate do not inhibit gastrin-II or histamine-stimulated secretion in duodenal ulcer patients after truncal vagotomy. Impairment of fat inhibition after truncal vagotomy or highly selective vagotomy in duodenal ulcer patients has been further reported by Lyndon and Johnston.<sup>11</sup> Before vagotomy 60 ml intraduodenal olive oil inhibited pentagastrin-stimulated secretion by 76% compared with 37% and 44% after truncal vagotomy and highly selective vagotomy respectively. However, in none of these studies<sup>7,8,11</sup> was fat inhibition evaluated in the same group of patients before and after vagotomy.

Fat-induced jejunal inhibition of gastric acid secretion was studied by Christiansen<sup>9</sup> in five patients before and after truncal vagotomy. It was concluded that fat inhibition was partly or wholly humorally mediated. Percentage inhibition was lower after truncal vagotomy, and it was considered that this was caused by the altered sensitivity of the parietal cells after vagotomy.

In the present study, the effect of a small volume of oleic acid—the smallest volume that evoked maximal inhibition in healthy subjects<sup>12</sup>—on a submaximal pentagastrin-stimulated gastric acid secretion was studied in the same group of duodenal ulcer patients before and after PGV. Postoperatively, a new three-dose pentagastrin test was carried out before oleic acid and control experiments. In two patients, a higher dose of pentagastrin was given

after PGV in order to compensate for a reduced sensitivity of the acid secretory glands to pentagastrin after the vagotomy. Before PGV, gastric acid secretion was inhibited by 25% after an intraduodenal oleic acid infusion. This inhibition was significantly less than that seen in a group of 11 healthy volunteers receiving the same amount of oleic acid.<sup>12</sup> The lower fat inhibition observed in duodenal ulcer patients compared with healthy subjects seems to be mainly due to a defective mechanism for fat inhibition. In a few duodenal ulcer patients a low duodenal pH may be a contributory factor (Table 1). Only two patients displayed consistently low duodenal pH in the oleic acid tests. A low duodenal pH may interfere with fat absorption by reducing the passage of fat into the micellar phase.<sup>16</sup> A low duodenal pH can activate an acid inhibitory mechanism,<sup>17,18</sup> which may, if encountered in both control and oleic acid experiments as in patient JOS (Table 1), also mask the fat-induced inhibition.

PGV abolished the fat-induced inhibition, and this abolition was sustained postoperatively even after the duodenal oleic acid load was increased to 40 ml (Fig. 3), indicating that an intact vagal innervation of the acid-secreting glands is a prerequisite for the inhibition of gastric acid secretion by low doses of fat, such as those met during physiological conditions. However, it is reasonable to assume that an additional increase of the duodenal fat load might evoke another, humoral inhibitory mechanism.

This may in turn explain the fat-induced inhibition observed after vagotomy in some studies<sup>8,11</sup> in accordance with the classical enterogastrone mechanism.<sup>4,19</sup>

The inhibition of gastric acid secretion brought about by an intraduodenal infusion of hypertonic solution has been claimed to be due to vagal reflex inhibition.<sup>20</sup> The fat inhibition observed in the present experiments did not appear until 30 to 45 minutes after the administration of the fat, which may be a questionable latency for a reflex inhibitory mechanism. A more intriguing explanation for the inhibitory mechanism is a fat-induced release of a hormone with the unique character of inhibiting only a vagally innervated gastric mucosa. Neurotensin is released by the oral ingestion of fat in man.<sup>21</sup> The exogenous infusion of this peptide in dogs inhibits the pentagastrin-induced gastric acid secretion from an innervated fundic pouch but is without an inhibitory effect after vagal denervation of the fundic pouch.<sup>22</sup>

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#### References

- <sup>1</sup>Ewald CA, Boas J. Beitrage zur Physiologie und Pathologie der Verdauung. *Virchows Arch [Pathol Anat]*, 1886; **104**: 271-305.
- <sup>2</sup>Bibler DD, Jr, Harkins HN, Nyhus LM. Inhibition of exogenous gastrin-stimulated gastric secretion by fat in the duodenum. *Rev Surg* 1965; **22**: 455-6.
- <sup>3</sup>Feng TP, Hou HC, Lim RKS. On the mechanism of the inhibition of gastric secretion by fat. *Chin J Physiol* 1929; **3**: 371-9.
- <sup>4</sup>Halvorsen HC, Middelton MD, Bibler DD, Jr, Harkins HN, Nyhus LM. Influence of the vagus nerve on the inhibitory effect of fat in the duodenum. *Am J Dig Dis* 1966; **11**: 911-7.
- <sup>5</sup>Konturek S, Grossman MI. Effect of perfusion of intestinal loops with acid, fat or dextrose on gastric secretion. *Gastroenterology* 1965; **49**: 481-9.
- <sup>6</sup>Sircus W. Studies on the mechanisms in the duodenum inhibiting gastric secretion. *Quart J exp Physiol* 1958; **43**: 114-33.
- <sup>7</sup>Johnston D, Duthie HL. Effect of fat in the duodenum on gastric acid secretion before and after vagotomy in man. *Scand J Gastroenterol* 1969; **4**: 561-7.
- <sup>8</sup>Ward AS. The effect of vagotomy on the inhibition of gastric secretion by intraduodenal fat. *Br J Surg* 1973; **60**: 533-6.
- <sup>9</sup>Christiansen J. Fat induced jejunal inhibition of gastric acid secretion in duodenal ulcer patients before and after truncal vagotomy. *Ann Surg* 1977; **186**: 573-6.
- <sup>10</sup>Gross RA, Isenberg JI, Hogan D, Samloff IM. Effect of fat on meal-stimulated duodenal acid load, duodenal pepsin load, and serum gastrin in duodenal ulcer and normal subjects. *Gastroenterology* 1978; **75**: 357-62.
- <sup>11</sup>Lyndon PJ, Johnston D. The effect of fat in the duodenum on gastric secretion before and after truncal vagotomy (TV) and highly selective vagotomy (HSV) in man. (Abstract). *Br J Surg* 1972; **59**: 905.
- <sup>12</sup>Kihl B, Olbe L. Inhibition of pentagastrin-stimulated gastric acid secretion by graded intraduodenal administration of oleic acid. *Scand J Gastroenterol*. (Accepted for publication).
- <sup>13</sup>Siegel S. *Nonparametric statistics for the behavioral sciences*. New York: McGraw Hill, 1956.
- <sup>14</sup>Stenquist B, Knutson U, Olbe L. The vagogastrone mechanism in man. *Scand J Gastroenterol* 1978; **13**: 895-901.
- <sup>15</sup>Stenquist B, Knutson U, Olbe L. Gastric acid responses to adequate and modified sham feeding and to insulin hypoglycemia in duodenal ulcer patients. *Scand J Gastroenterol* 1978; **13**: 357-62.
- <sup>16</sup>Go VLW, Poley JR, Hofmann AF, Summerskill WHJ. Disturbances in fat digestion induced by acidic jejunal pH due to gastric hypersecretion in man. *Gastroenterology* 1970; **58**: 638-46.
- <sup>17</sup>Grossman MI *et al.*: Candidate hormones of the gut. *Gastroenterology* 1974; **67**: 730-55.
- <sup>18</sup>Wormsley KG. The pathophysiology of duodenal ulceration. *Gut* 1974; **15**: 59-81.
- <sup>19</sup>Kosaka T, Lim RKS. Demonstration of the humoral agent in fat inhibition of gastric secretion. *Proc Soc Exp Biol Med* 1930; **27**: 890-1.
- <sup>20</sup>Ward AS. Effect of vagotomy on the gastric secretory response to intraduodenal osmotic agents in man. *Gut* 1976; **17**: 48-53.
- <sup>21</sup>Rosell S, Rökaeus Å. The effect of ingestion of amino acids, glucose and fat on circulating neurotensin-like immunoreactivity (NTLI) in man. *Acta Physiol Scand* 1979; **107**: 263-7.
- <sup>22</sup>Andersson S, Rosell S, Sjödin L, Chang D, Folkers K. Inhibition of acid secretion from vagally innervated and denervated gastric pouches by (Gln<sup>4</sup>)-neurotensin. *Scand J Gastroenterol* (In press).