Basal and Meat Extract Plasma Gastrin Before and After Parietal Cell Vagotomy and Selective Gastric Vagotomy with Drainage in Patients with Duodenal Ulcer

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Basal and meat extract stimulated plasma gastrin (PG) levels and basal and stimulated gastric acid secretion were evaluated pre and postoperatively in duodenal ulcer patients who underwent parietal cell vagotomy without antral drainage (normal duodena) (PC, n = 32) or selective vagotomy with drainage (pyloric stenosis) (SV + P, n = 11). Before operation, both groups had comparable basal PG values of 52 ± 13 pg/ml (PCV) and 51 ± 18 pg/ml (SV + P), while the peak gastrin level to meat extract stimulation was 173 ± 40 pg/ml for the total group of patients. After both operations basal PG levels increased (107 ± 18 pg/ml (PCV) and 152 ± 45 pg/ml (SV + P)) and the gastrin response to meat extract stimulation was augmented after PCV, while the response after SV + P was the same as before operation. Patients with PCV often demonstrated an acid response following meat extract stimulation (3.6 ± 0.9 mEq HCl/hr), and pentapeptide stimulation (18.8 ± 2.0 mEq/hr) while patients with SV + P showed a minimal response (1.3 ± 1.2 mEq HCl/hr meat extract), and 10.7 ± 1.8 mEq/hr pentapeptide stimulation. The comparatively intact acid responses in the PCV patients may augur a high ultimate recurrence rate.

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IN THE PAST DECADE, operations for duodenal ulcer have become more conservative of gastric mass with a tendency to interfere less with physiologic function. Associated with this has been an apparent increase in recurrence of duodenal ulcer,[11,12,34] especially following vagotomy and drainage as compared with hemigastrectomy or antrectomy with vagotomy.[12,26] The newest of these gastric-mass-conserving operations, parietal cell vagotomy without drainage in patients without pyloric stenosis has enjoyed popularity in England and Europe.[1,3,25] It appears to give early clinical results which are quite satisfactory and without interference in gastric emptying.[1,7,21]

The physiological principle of this operation is that while the parietal cell mass of the stomach is denervated, the antrum is left innervated and drainage is not required. While insulin-stimulated acid secretion often disappears and stomach emptying is normal after PCV in dogs,[1] this operation results in an enhanced acid response to feeding and an aproximately 50% increase of the 24 hour Heidenhahn Pouch acid secretion,[1,2] suggesting increased secretion of antral gastrin.

In the following study, basal and meat extract stimulated plasma gastrin (PG) levels pre and postoperatively and acid secretion in response to insulin hypoglycemia, pentagastrin, and meat extract stimulation were evaluated in duodenal ulcer patients before and after parietal cell vagotomy (PCV), and in those patients with pyloric stenosis, selective vagotomy and pyloroplasty (SV + P). Postoperatively, patients were divided into insulin negative and insulin positive groups, and the co-variation of the meat extract stimulated acid secretion and plasma gastrin levels determined. The results indicate that considerable acid secretion responsiveness remains after parietal cell vagotomy, and that this may be correlated with the elevated levels of gastrin seen in response to meat extract stimulation.

Material and Methods

Forty-three patients were studied at the Kommune Hospital in Copenhagen, Denmark, 5 women and 39 men, with a mean age of 57 years (range 22–76 years). At operation, a duodenal ulcer was found in 42 patients and no ulcer in 1 patient. In 32 patients in whom no pyloric

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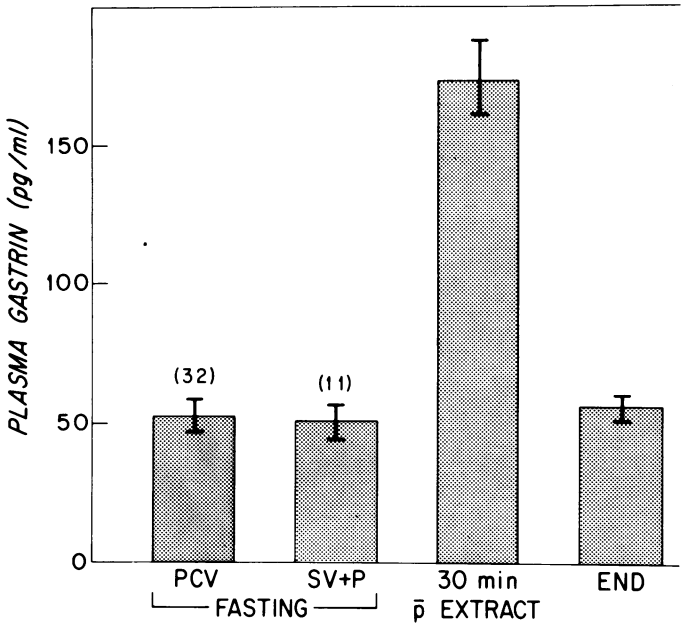

FIG. 1. Mean basal plasma gastrin levels ± SEM in both groups of patients and mean meat extract stimulated plasma gastrin ±SEM of the total number of patients before operation. Number of patients in each group are given in parenthesis.

stenosis was found, PCV was performed while in 11 patients with varying degrees of pyloric stenosis, SV + P was performed.

Samples for fasting PG were drawn on two separate occasions in 43 patients before operation and in 36 patients between 2 and 3 months after operation. Meat extract stimulation, which was done in 25 patients before operation and in 21 patients after operation, was only slightly modified.[10] PG samples were obtained 30 minutes after the meat extract stimulation, and at the end of the stimulation. The gastrin levels were measured by a sensitive radioimmunoassay method.[9] The samples were coded by number and the code broken only after the results were recorded. Each sample was assayed at least twice.

Gastrin Radioimmunoassay

Preparation of antigen was similar to that described by McGuigan.[35] Five mg of synthetic human gastrin, residues 2–17 (2–17 SHG, Imperial Chemical Industries) were added to approximately 2.2 × 10^6 cpm of labelled ^{125}I 2–17 SHG, and mixed with 10 mg bovine serum albumin in 0.33 ml 0.05 M pH 7.4 potassium phosphate buffer. Carbodiimide, (1-ethyl-3) (-3-dimethyl-aminopropyl) 42 mg was added and the reaction allowed to proceed for 20 hr at 20 C. After dialysis for 24 hr, approximately 9.3 moles of 2–17 SHG were coupled per mole of bovine serum albumin. The conjugated material was mixed with Freund's adjuvant and injected into the toepads of four rabbits. Rabbits received booster shots 6 months later and were bled 7 days later via the central ear artery. Serum obtained from one of the four rabbits was used as antibody in a final dilution of 1:150,000.

For the radioiodination of gastrin 1 ug SHG 1–17 was added with 100 μl pH 7 0.5 M phosphate buffer to 2 mCi carrier-free ^{125}I in 8 μl NaOH. Chloramine-T was used as an oxidizing agent. The reaction was allowed to proceed for 60 seconds according to the method of Hunter and Greenwood.[20] Sodium bisulphite (2.5 mg/ml) in pH 7.4 0.5 M phosphate buffer was used to stop the reaction. The resultant product was then applied at 4 C to a G10 Sephadex column of 12 ml capacity with a drip rate of approximately 1 per 20 seconds. The labelled peptide appeared in the void volume. Estimated specific activity was generally 250 mCi/mg. The labelled peptide was then further purified by starch gel electrophoresis.

Assay Technique

Incubation components of the radioimmunoassay for gastrin were 50 μl of the plasma sample to be assayed, 250 μl 0.02 M Barbital buffer (pH 8.2), 2,000 cpm ^{125}I 1–17:SHG in 100 μl Barbital buffer and 100 μl 1:30,000

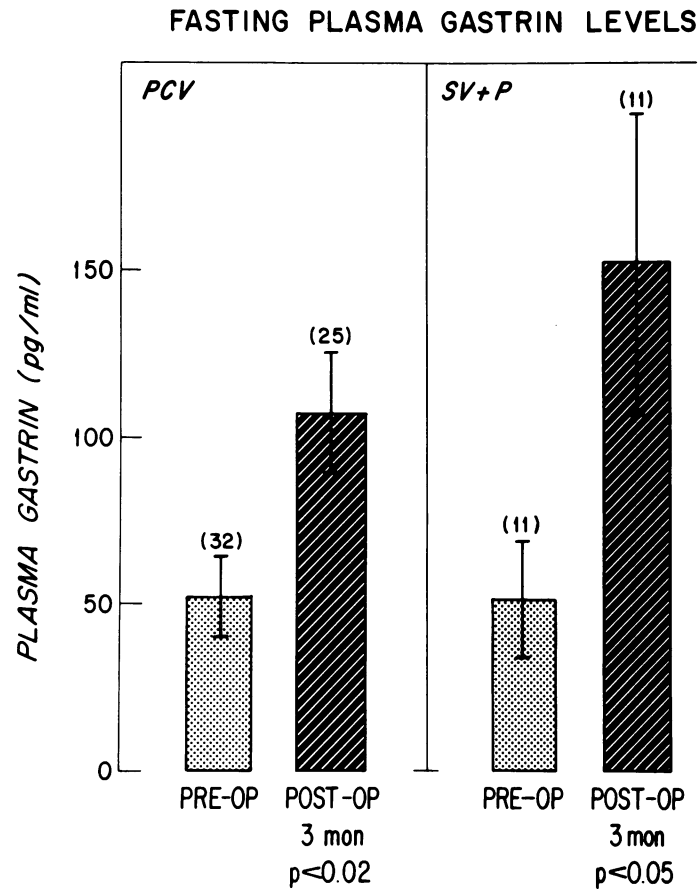

FIG. 2. Mean basal plasma gastrin levels ± SEM pre and postoperatively in both groups of patients (PCV and SV ± P). Numbers of patients in each group are given in parenthesis.

rabbit antigastrin antibody, making a final antibody dilution of 1:150,000. The mixture was incubated for up to 4 days at 4 C. Separation was achieved with 200 μl dextran-coated charcoal, supernatant decanted after centrifugation, and both bound and free components counted. Determinations were carried out in triplicate, with triplicate "damage" tubes to which no antibody had been added. Standard curves were obtained by adding known quantities of SHG 1:17 to human plasma which had been rendered gastrin-free by washing with dextran-coated charcoal. The coefficient of variation for the assay using this technique was 5 ± 1.3%. By this technique, gastrin can be accurately assayed from 16–1,000 pg/ml and levels above 1,000 pg/ml can be measured by dilution of the plasma sample with degastrinized plasma. The normal values for plasma gastrin (PG) levels were 0–150 pg/ml; approximately 35% of patients without demonstrable gastrointestinal disease have undetectable values (less than 16 pg/ml).

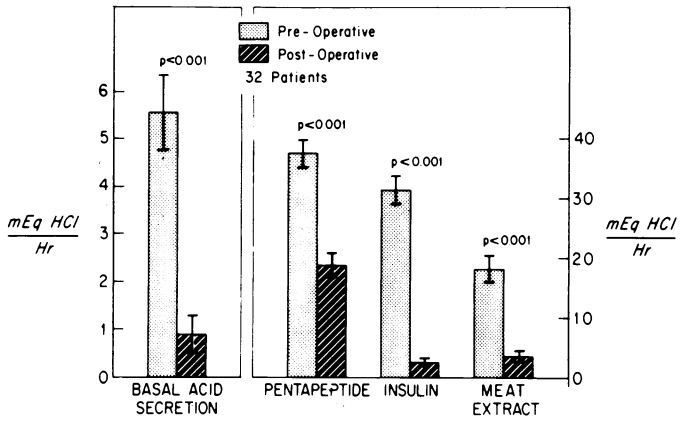

FIG. 4. Mean basal stimulated gastric acid secretion in response to pentagastrin, insulin hypoglycemia and meat extract pre and postoperatively in the parietal cell vagotomy group. Although there were 32 patients in the entire group, not all patients underwent testing pre and postoperatively. The numbers of patients in whom each test was carried out are given in the text.

Gastric Acid Secretion

Gastric acid secretion studies were carried out preoperatively and between two and three months postoperatively.

The pentapeptide test was performed by stimulation with 6 microgram Peptavlon (ICI)/kg sc before the operation (25 patients) and with 10 microgram Peptavlon/g sc after the operation (19 patients). These doses have previously been shown to elicit maximal acid output both before and after PCV.[25] The insulin test was performed by stimulation with 0.2 IU/kg iv in 12 patients before and in 22 patients after operation.

The meat extract test was done in 25 patients before and in 21 patients after operation, only slightly modified after Giles and Clark (1966). Three oxo cubes were dissolved in 200 ml warm water and pH adjusted to 7.0 by adding 15–20 ml of 8% sodium bicarbonate. This solution was introduced into the stomach via nasogastric tube and left in the stomach 15 minutes with the patient in a sitting position. The stomach was then emptied by 5 minute aspirations with the patient supine. The stomach was rinsed with 200 ml of water and emptied by a further 5 minute aspiration. The entire procedure lasted about 30 minutes.

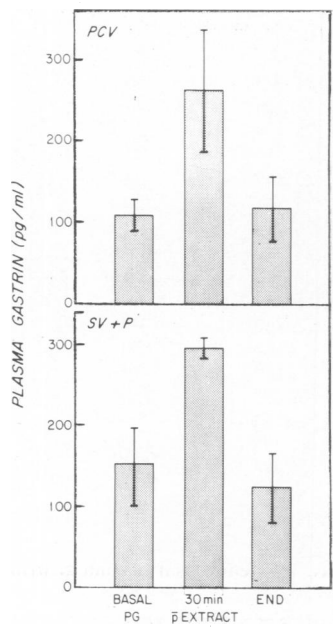

FIG. 3. Mean basal and meat extract stimulated plasma gastrin levels ± SEM postoperatively in both groups of patients (PCV and SV + P).

All tests were done after an overnight fast. Gastric tubes were placed under fluoroscopic control with the patients supine. Aspiration was performed by intermittent pump suction, which was constantly supervised; aspirates were collected every 15 minutes.

For meat extract stimulation, the first 15 minute aspirate obtained before stimulation was designated "fasting secretion" and the next four 15 minute aspirates designated "basal secretion."

After pentapeptide or meat extract stimulation, six 15 minute aspirates were collected. After insulin, there were nine 15 minute aspirate collections. For each 15 minute aspirate, volume, pH (Radiometer) and acidity (by Titration to pH 7.0) were measured. Maximal acid production is expressed as "peak acid output" (PAO), the highest acid production in two consecutive 15 minute periods multiplied by two (mEq/hr). There was undoubtedly some loss of acid secretion, especially after SV + P, but no attempt was made to correct for this.

Statistical treatment of the results involved the calculation of mean values and standard errors of the mean and statistical analysis of differences in group means, was by use of unpaired Student's *t*-test. In the text, data are

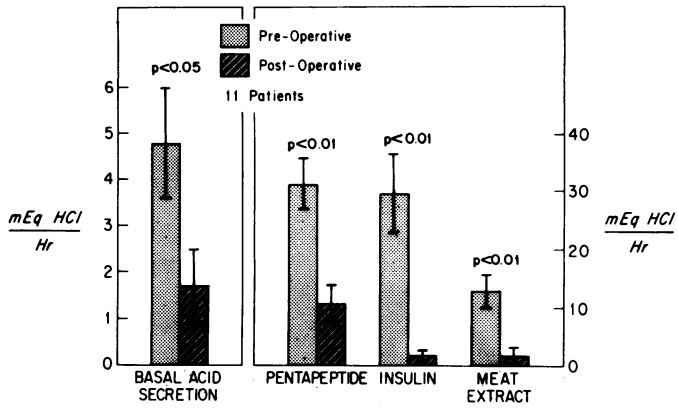

FIG. 5. Mean basal and stimulated gastric acid secretion in response to pentagastrin, insulin hypoglycemia and meat extract pre and postoperatively in the group who underwent selective vagotomy and pyloroplasty. Eleven patients are included in the total group. All underwent all tests before and after operation.

given as a mean ± SEM and wherever the word "significant" is used, it indicates a calculated P value of less than 0.05.

Results

Preoperatively, both groups had comparable mean basal PG values of 52 ± 13 pg/ml (n = 32) in the group that underwent PCV, and 51 ± 18 pg/ml (n = 11) in the patients in whom SV + P was performed. After stimulation with meat extract, the mean PG value of the total group of patients had risen 30 minutes after stimulation to 173 ± 40 pg/ml (Fig. 1). By 90 minutes, this had fallen to a mean of 56 ± 10 pg/ml, almost exactly the basal level.

Postoperatively, the mean basal PG increased significantly in both groups to 107 ± 18 pg/ml ($P < 0.02$) in the PCV group and to 152 ± 45 pg/ml ($P < 0.05$) in the SV + P groups (Fig. 2). There was a considerable gastrin response to the meat extract stimulation after both operations. The mean basal PG rose to 260 ± 74 pg/ml, 30 minutes after stimulation in the PCV group, while after SV + P the PG rose to 300 ± 13 pg/ml (Fig. 3). After 90 minutes, PG levels returned to 117 ± 38 pg/ml (PCV) and 126 ± 44 pg/ml (SV + P). When the gastrin response to meat extract stimulation is defined as the peak PG level after stimulation minus the basal PG level, the mean gastrin response after PCV was 160 pg/ml, in comparison to preoperative values 118 pg/ml, but the difference was not significant ($P = 0.60$). Gastrin response to meat extract stimulation after PCV was not significantly different from after SV + P ($P = 0.50$).

Following operation, acid secretion response to all stimuli was decreased. Basal acid secretion (BAO) in the PCV group was only 0.9 ± .04 mEq/hr and rose to 3.6 ± 0.9 mEq/hr after meat extract stimulation, and to 18.8 ± 2.0 mEq/hr after pentapeptide stimulation. Insulin stimulated secretion fell to 2.5 ± 0.7 mEq/hr (92% reduction), the greatest reduction of all groups (Fig. 4). In the SV + P group, BAO was 1.7 ± 0.8 mEq/hr. Following insulin stimulation, only 1.1 ± 0.6 mEq/hr was secreted and following meat extract stimulation, 1.3 ± 1.2 mEq/hr (Fig. 5). When patients were grouped postoperatively according to their insulin test, there was no significant difference in basal and meat extract stimulated PG levels between insulin negative and insulin positive patients in both groups (Table 1). After PCV, however, there was a positive relationship (correlation coefficient = 0.62) between meat extract stimulated PG levels and gastric acid response (Fig. 6) with a slope significantly different from zero at the $P = 0.05$ level.

Discussion

In spite of the demonstrated low recurrence rate following hemigastrectomy and vagotomy,[12,17,26] the occasional poor result following major gastric resection, especially in the underweight female, has led many investigators to seek operations for peptic ulcer which, while reducing the acid producing capacity of the stomach are conservative of gastric mass. The newest of these operations is the parietal cell vagotomy, in which the parietal cell mass is denervated while the motor innervation of the antrum, which aids gastric emptying, is

TABLE 1. *PG Levels and Gastric Acid Secretion 2–3 Months after PCV And SV + P*

Patient No.	Basal PG (pg/ml)	PG 1 Hr. After Meat Extract Stimulation (pg/ml)	Basal Acid Secretion (mEq/hr)	Acid Secretion 1 Hr. After Meat Extract (mEq/hr)
After PCV				
7.615 – I	85	240	0	0
24.809	60	165	0	3.7
25.326	125	450	0	8.1
25.728	20	170	0	3.2
25.746	25	300	0	4.8
25.868	38	210	0	9.8
25.947	20	100	0	0.1
26.076	20	130	0	0
26.422	100	200	0.4	6.1
26.498	200	250	0	0
After PCV				
25.730 + I	49	50	0.2	1.5
26.158	70	140	0.2	1.1
26.160	70	215	0	1.9
26.402	350	1240	4.5	9.8
After SV + P				
24.776 – I	100	—	0	0
25.646	120	20	0.7	0
26.012	20	150	0.2	0
After SV + P				
25.643 + I	145	210	0	0
25.682	510	800	2.0	0.4
26.543	130	320	7.5	7.7

Note: –I = insulin negative; +I = insulin positive.

left intact, as is the neural arc in the release of antral gastrin. Acid inhibition from the parietal cell mass, the most potent feedback mechanism inhibiting the release of antral gastrin, is diminished. This would seem, superficially at least, a possible ulcerogenic situation, but the early reports, notably from centers in England and Scandinavia have been enthusiastic.[4,8,19,23,25,32,41] While sufficient time has not elapsed for late recurrences, the early recurrence rate is still very low and well below the 2% level,[13,16,18,25] except for one recent report.[27]

The results reported herein confirm that in a group of ulcer patients whose preoperative fasting PG does not differ significantly from basal levels in other patients with duodenal ulcer,[36,39,40] fasting plasma gastrin increases significantly following parietal cell vagotomy.[22,31,33,38] The data are still only at variance with those reported by Clark, *et al.*[6] The gastrin response to meat extract stimulation was increased after PCV and remained unchanged after SV + P. This is in accordance with the findings of Jaffe, et al.[22] and again at variance with the findings of Clark and co-workers,[6] who found a decrease in gastrin response to oxo-meat extract stimulation after PCV. These results need not be surprising, as it has been amply demonstrated that different laboratories using different antibodies, or indeed the same laboratory using different antibodies[15] may be measuring different components of circulating gastrin, and that these components presumably change with stimulation.

After truncal, selective and parietal cell vagotomy, basal plasma gastrin levels are increased significantly, perhaps because of the reduction of acid inhibition[14,30] and after truncal vagotomy, probably also due to section of extra gastric vagal fibers.[28,31] Although gastrin released from duodenal and other sources may be increased following vagotomy, this form of gastrin may perhaps be less potent in evoking acid production. Since column chromatography of the gastrin released was not carried out in our study, the molecular species is unknown (Berson and Yalow, 1971), and this must remain conjecture.

There is a positive correlation between the elevated levels of circulating gastrin and the acid production in response to an oxo-meat extract stimulation at 2 to 3 months following PCV, but acid secretion in response to a variety of stimuli appears to be reduced and parietal cell responsiveness is a fraction of what it was previous to operation. After both operations, the gastrin response to meat extract stimulation is the same in insulin positive and insulin negative patients (Table 1). Only in the 3 insulin negative patients after SV + P is there no acid response to meat extract stimulation, with a positive acid response in the insulin positive patients. However, the number of patients is too small to draw any conclusions.

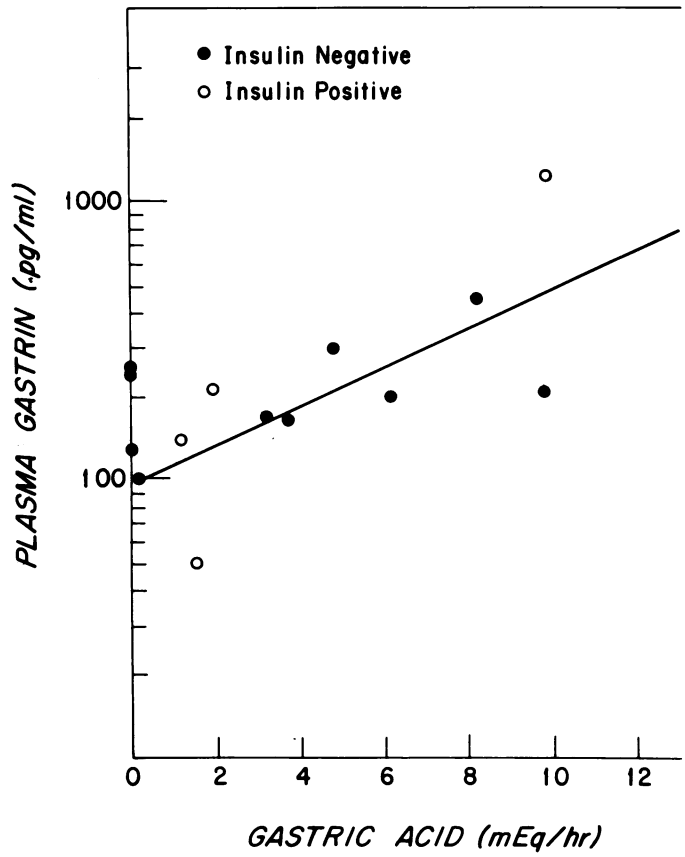

FIG. 6. Relationship between meat extract stimulated plasma gastrin levels (peak response) and gastric acid response in a group of patients who had undergone parietal cell vagotomy. There is no difference between the insulin positive and insulin negative patients, and a correlation coefficient of 0.62 is apparent, yielding a slope significantly different from zero at the P = 0.05 level.

After PCV, the meat extract stimulated acid secretion is not separable on the basis of insulin positivity or insulin negativity, a finding of potential importance, since the number of insulin positive patients appears to increase in time and may exceed 50% at times greater than one year following parietal cell vagotomy.[5] It also suggests that the release of gastrin after meat extract stimulation is more important than vagal innervation for the stimulation of gastric acid secretion.

A recent demonstration of reinnervation of the parietal cells at periods of time of greater than a year following parietal cell vagotomy with an associated increase in peak acid output following pentagastrin stimulation[5] makes one wonder whether in fact continued conversion of patients from insulin negative to insulin positive will not yield an increased acid secretion close to that of the preoperative levels. (The most recently available figures suggest a close to 70% positive Hollander Test at the end of 2 years. Acid secretory capacity is about 60–70% preoperative capacity. D. Johnston and J. C. Goligher, personal communication.)

Despite indications that the acid relieving benefits of parietal cell vagotomy may be temporary, and that increased parietal cell responsiveness combined with increased circulating basal and stimulated gastrin may lead to increased acid production, the early clinical results continue to be excellent. It should be noted, however, that similar enthusiasm followed the introduction of posterior gastrojejunostomy, and that the mean time of recurrence which, ultimately, was as high as 30%, was approximately 13 years after the performance of the initial procedure.[37] Moreover, the patients with normal duodena operated on in most of these series appear to be a group of patients at an earlier stage of their disease than those patients with scarred duodena generally operated on in the United States. While it is impossible to predict the effects of stage of disease upon time of recurrence, it would be logical to assume that those patients at an earlier stage in the peptic ulcer disease perhaps might recur at a later date and form a more favorable group for early operation. Thus, although the data reported here and in other series give cause for concern, the prospective trials now in progress in a variety of centers appear to be well justified, since the benefits of this operation as far as preservation of normal physiology and gastric emptying and possible late nutritional effects may be important.

Finally, these experiments demonstrate that in man the primary determinant of gastric acid secretion appears to be parietal cell responsiveness, and that in spite of the release of large quantities of presumably potent antral gastrin, both in the basal state and in response to food, acid production is not increased in these patients. Although a correlation may be demonstrated between gastrin and acid secretion, the dose response curve is shifted far to the right with a denervated parietal cell mass.

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