

Serum gastrin in duodenal ulcer

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Part III Influence of vagotomy and pylorotomy

SUMMARY Following truncal vagotomy and anterior pylorotomy for duodenal ulcer, fasting serum gastrin levels were higher at 84 ± 7.9 pg per ml than in unoperated patients with duodenal ulcer (16 ± 1.5 pg per ml). In response to a standard protein meal, the peak serum gastrin achieved in the vagotomized group was 259 ± 37.8 pg per ml at 75 minutes after ingestion, a much higher response than that obtained with a standard meal plus prior atropinization in the unoperated duodenal ulcer patients.

These results suggest that truncal vagotomy allows release of gastrin which was previously inhibited with the vagi intact and the temporal characteristics of the response indicate that some of this gastrin is derived from an extragastric source. The results also exemplify the dependence of gastrin estimations as measured by this immunoassay on the acidity of the contents bathing the gastric antrum.

The two companion communications in this issue have shown that basal serum gastrin is in the low part of the normal range in duodenal ulcer and have provided evidence for an increased G cell population by food and vagal stimulation studies (Hansky, Korman, Cowley, and Baron, 1971a; Korman, Soveny, and Hansky, 1971a). It is considered that the low normal serum gastrin is due to strong inhibition by the acid milieu in the antrum. It has also been shown that modification of this inhibitory mechanism leads to a greatly increased release of gastrin in response to exogenous stimulation.

If these proposals are correct, then vagotomy and drainage may be expected to cause basal serum gastrin levels to be raised in this disease because of removal of inhibitory factors. In addition, food stimulation could provide an analogous situation to that achieved by food and atropinization unless the vagotomy has resulted in diminished antral gastrin.

This communication reports serum gastrin levels in duodenal ulcer patients after truncal vagotomy and pylorotomy in the basal state and following a standard protein meal stimulus.

Material and Methods

After an overnight fast 50 patients who had undergone vagotomy and pylorotomy had blood drawn

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for gastrin determination. All patients had been treated for a long history of dyspepsia before surgery and the indication for surgery was failure of adequate medical treatment to control symptoms. Surgery had taken place from three months to seven years before gastrin determination and in all patients the procedure had been bilateral truncal vagotomy and anterior pylorotomy (Scott, 1968).

Eleven females and thirty-nine males comprised the group studied and the mean age was 46 years with a range from 33 to 67 years. Twenty-one patients had been investigated for completeness of vagotomy by the insulin hypoglycaemia test (Hollander, 1946) and all but one of these patients had a complete vagotomy.

Five patients from the group having evidence by the Hollander test of a complete vagotomy were then investigated after an overnight fast. Each patient was given a protein stimulus comprising a meal of steak, cheese, and milk (protein 60 g, fat 51 g, and carbohydrate 11 g). Peripheral venous blood was collected at -30, 0, 15, 30, 45, 60, 75, 90, 105, and 120 minutes after protein.

An additional five patients with active duodenal ulcer were studied. All had positive radiographs and surgical management was necessary because adequate medical therapy had failed to relieve pain or there was current gastrointestinal haemorrhage. Each patient underwent vagotomy and anterior

pylorectomy, and fasting blood was collected for gastrin estimation just before operation and daily after the operation for one week.

The serum was separated by centrifugation and gastrin determined by immunoassay (Hansky and Cain, 1969; Hansky, Soveny, and Korman, 1971b). Statistical analysis was by the use of Student's *t* test for group means using standard formulae (Snedecor and Cochran, 1967).

Results

The mean \pm SEM basal gastrin in the 50 patients who had undergone vagotomy and pylorectomy was 84 ± 7.9 pg/ml (range 30 – 420 pg/ml), this level being significantly higher than in a group of 72 patients with duodenal ulcer (unoperated) whose basal gastrin level was 15.7 ± 1.5 pg/ml ($P < 0.0005$).

The mean gastrin level for the 11 females was similar to the group as a whole at 84 ± 12.1 pg/ml. The 20 patients in whom the Hollander test had shown evidence of complete vagotomy had a gastrin level similar to the whole group at 81 ± 6.4 pg/ml. The serum gastrin of the one patient with Hollander test evidence of an incomplete vagotomy was 52 pg/ml.

Gastrin levels related to the date of operation showed no difference between groups operated on recently compared to groups operated on seven years previously.

Figure 1 shows the serum gastrin response in five patients to a protein meal stimulus. The serum gastrin level rose significantly from a basal level of 74 ± 7.6 pg/ml to a peak of 259 ± 37.8 pg/ml at 75 minutes after protein ($P < 0.0025$) and was significantly raised at the completion of the study (two hours) at 191 ± 23.3 pg/ml ($P < 0.0025$). Corresponding figures for unoperated duodenal ulcer patients and normal subjects with prior atropinization are shown on the graph for comparison. The rise above basal levels is significantly higher in the vagotomy group than in either unoperated patients ($P < 0.05$) or normal subjects ($P < 0.001$).

Table I shows the preoperative and serial post-operative basal serum gastrin levels in the five

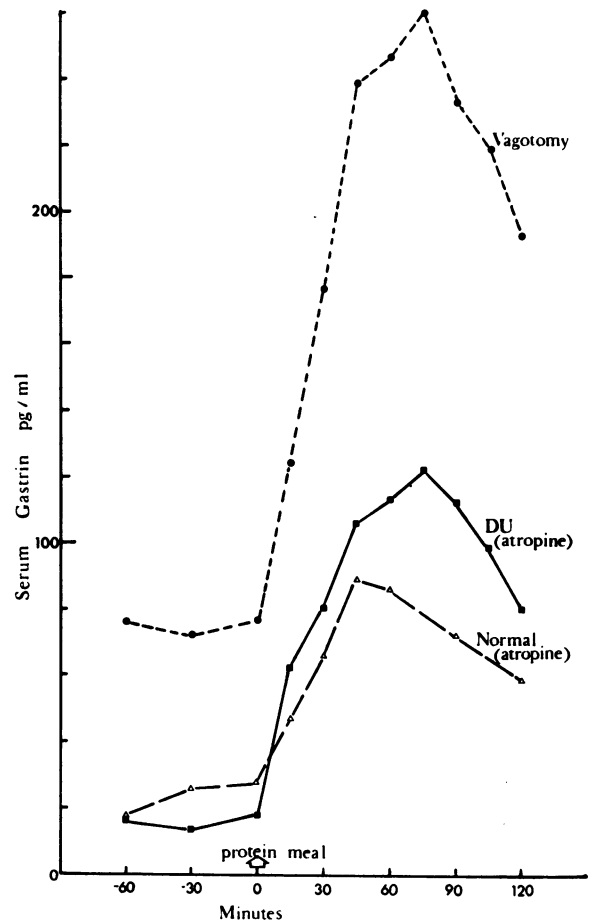


Fig. Serum gastrin in response to protein meal stimulus in patients after truncal vagotomy compared with the response to a similar meal with prior atropinization in normal subjects and patients with active duodenal ulcer. Points represent the mean of five, 10, and five patient studies respectively.

Preoperative Gastrin (pg/ml)	Time Postoperatively (days)							
	1	2	3	4	5	6	7	
Mean	12	109	94	110	117	97	97	101
SEM	2.7	5.4	12.4	12.6	12.6	6.2	3.9	3.7
P ¹		<0.0005	<0.01	<0.0005	<0.001	<0.001	<0.001	<0.001

Table I Basal serum gastrin after truncal vagotomy in five patients with duodenal ulcer

¹P = significance of difference from preoperative levels: <0.05 significant.

patients who were followed daily after truncal vagotomy. Gastrin rose significantly from a basal level of 12 ± 2.7 pg/ml to one of 109 ± 5.4 pg/ml on the first postoperative day and remained significantly elevated for the remainder of the study.

Discussion

Bilateral truncal vagotomy with anterior pylorotomy produces a significant rise in basal levels of gastrin above those found in either normal subjects or unoperated patients with duodenal ulcer. This rise in gastrin is found within 24 hours of surgery.

It is considered that this is partly due to removal of acid inhibition by vagal section and duodenal reflux which permits increased release of gastrin. That this is not the sole factor responsible for the increased gastrin in vagotomized patients is illustrated by a comparison of gastrin levels in these patients and in unoperated duodenal ulcer patients. Neutralization of antral contents with bicarbonate in unoperated duodenal ulcer patients raises the serum gastrin level to about 45 pg/ml (Hansky *et al.*, 1971a) and this is below the mean basal level of 84 pg/ml in vagotomized patients. This indicates the extra release of gastrin, above that which could be achieved by the role of vagal section and duodenal reflux in neutralization of the antrum, and this may be from an extragastric source.

This raises the question as to the role of the vagus in gastric secretion. That the vagus acts on the antrum to release gastrin and on the parietal cell to release acid is well known (Korman, Soveny, and Hansky, 1971b; Pevsner and Grossman, 1955). Its role in the inhibition of gastric secretion is less well understood. Stening and Grossman (1970) have shown that extragastric vagotomy in dogs increases the response of a Heidenhain pouch to pentagastrin but not to histamine. It has also been shown that this increases the spontaneous 24-hour acid output from vagally denervated Heidenhain pouches (Kelly, Nyhus, and Harkins, 1964; Landor, 1964; Middleton, Kelly, Nyhus, and Harkins, 1965). Further Middleton *et al.* (1965) showed that dogs with denervated pouches, total gastrectomy, and truncal vagotomy increased pouch secretion in response to a meal as compared to the situation when the extragastric fibres were intact. They suggested that extragastric vagotomy may produce intestinal stasis and release of intestinal gastrin. Emås and Grossman (1969) have suggested that an inhibitor under vagal control may be present and this no longer acts when the vagi are sectioned.

Added evidence for an extragastric source of gastrin is provided by the protein meal studies. In the unoperated duodenal ulcer patients, a protein

meal alone raises the serum gastrin by 77 pg/ml at 45 minutes after ingestion and with prior atropine raises it by 107 pg/ml at 75 minutes whereas in the vagotomized patients the rise is 185 pg/ml at 75 minutes which is significantly greater than the previously achieved levels.

In an effort to explain these findings of an increased response to food after vagotomy, occurring at a later time than in the unoperated patient, the most likely explanation is that truncal vagotomy causes a decrease in a factor whose main function is to inhibit gastrin release from the duodenum and/or small intestine. Berson and Yalow (1971) and Emås, Borg, and Fyrö (1971) have shown the presence of gastrin in the duodenum by immunochemical and bioassay means and so the increased gastrin response to food in this study may be derived, not only from the antrum, but also from the duodenum. This is supported by the finding of an increase in serum gastrin in response to food in a patient who had an antrectomy and truncal vagotomy whereas no such increase is found in patients with standard Polya gastrectomy and no vagotomy (J. Hansky and M. G. Korman, unpublished observation). This hypothesis will be answered by study of gastrin release in patients who have had a selective vagotomy.

Other possible explanations for the increased response to food after truncal vagotomy may be that gastrin release from the antrum is controlled by an intragastric factor, other than acid, associated with the parietal cell (Korman, Strickland, and Hansky, 1971c) and vagotomy causes decreased release of this factor. Finally it has been shown that secretin causes a fall in serum gastrin levels (Hansky *et al.*, 1971b), but evidence indicates that truncal vagotomy does not interfere with secretin release (Stening and Grossman, 1970).

The value of serum gastrin estimations in the assessment of completeness or otherwise of the vagotomy cannot be deduced from these results. Of the 50 subjects studied, 21 were tested postoperatively by the Hollander test and one was found to have an incomplete vagotomy. His basal serum gastrin level was 52 pg/ml as compared with the group mean of 84 pg/ml but gastrin was still within the post-vagotomy range.

Byrnes, Lazarus, and Young (1970) are the only other group to have reported postvagotomy findings and their results are diametrically opposed to the present ones. That they are measuring a different gastrin or peptide is quite evident, and we believe that they may have found a component of 'gastrin' which is pathological, removed by complete vagotomy, and present in most patients with duodenal ulcer. Certainly the present assay cannot detect this 'gastrin', but does detect gastrin which behaves

physiologically in the same manner, as indirect evidence in animals suggests that gastrin should function (Pe Thein and Schofield, 1959; Posey and Franklin, 1967).

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References

- Berson, S. A., and Yalow, R. S. (1971). Nature of immunoreactive gastrin extracted from tissues of gastrointestinal tract. *Gastroenterology*, **60**, 215-222.
- Byrnes, D. J., Lazarus, L., and Young, J. D. (1970). Effect of vagotomy on serum gastrin in patients with duodenal ulceration. *Aust. Ann. Med.*, **19**, 240-243.
- Emås, S., Borg, I., and Fyrö, B. (1971). Antral and duodenal gastrin activity in non-ulcer and ulcer patients. *Scand. J. Gastroent.*, **6**, 39-43.
- Emås, S., and Grossman, M. I. (1969). Response of Heidenhain pouch to histamine, gastrin and feeding before and after truncal vagotomy in dogs. *Scand. J. Gastroent.*, **4**, 497-503.
- Hansky, J., and Cain, M. D. (1969). Radioimmunoassay of gastrin in human serum. *Lancet*, **2**, 1388-1390.
- Hansky, J., Korman, M. G., Cowley, D. J., and Baron, J. H. (1971a). Serum gastrin in duodenal ulcer: II. Effect of insulin hypoglycaemia. *Gut*, **12**, 959-962.
- Hansky, J., Soveny, C., and Korman, M. G. (1971b). Effect of secretin on serum gastrin as measured by radioimmunoassay. *Gastroenterology*, **61**, 62-68.
- Hollander, F. (1946). The insulin test for the presence of intact nerve fibres after vagal operations for peptic ulcer. *Gastroenterology*, **7**, 607-614.
- Kelly, K. A., Nyhus, L. M., and Harkins, H. N. (1964). The vagal nerve and the intestinal phase of gastric secretion. *Gastroenterology*, **46**, 163-166.
- Korman, M. G., Soveny, C., and Hansky, J. (1971a). Serum gastrin in duodenal ulcer: I. Basal levels and the effect of food and atropine. *Gut*, **12**, 899-902.
- Korman, M. G., Soveny, C., and Hansky, J. (1971b). Radioimmunoassay of gastrin: The response of serum gastrin to insulin hypoglycaemia. *Scand. J. Gastroent.*, **6**, 71-75.
- Korman, M. G., Strickland, R. G., and Hansky, J. (1971c). Serum gastrin in chronic gastritis. *Brit. med. J.*, **2**, 16-18.
- Landor, J. H. (1964). The effect of extragastric vagotomy on Heidenhain pouch secretion in dogs. *Amer. J. dig. Dis.*, **9**, 256-262.
- Middleton, M. D., Kelly, K. A., Nyhus, L. M., and Harkins, H. N. (1965). Selective vagal effects on the intestinal phase of gastric secretion. *Gut*, **6**, 296-300.
- Pe Thein, M., and Schofield, B. (1959). Release of gastrin from the pyloric antrum following vagal stimulation by sham feeding in dogs. *J. Physiol. (Lond.)*, **148**, 291-305.
- Pevsner, L., and Grossman, M. I. (1955). The mechanism of vagal stimulation of gastric acid secretion. *Gastroenterology*, **28**, 493-499.
- Posey, E. L., Jr., and Franklin, H. (1967). Relation of antral pH to gastrin release and fundal pH in dogs. *Amer. J. dig. Dis.*, **12**, 356-362.
- Scott, P. R. (1968). Vagotomy and anterior pylorotomy for uncomplicated duodenal ulceration: results of 38 cases. *Aust. N.Z. J. Surg.*, **38**, 141-143.
- Snedecor, G. W., and Cochran, W. G. (1967). *Statistical Methods*, 6th ed., pp. 91-119. Iowa State University Press. Ames, Iowa.
- Stening, G. F., and Grossman, M. I. (1970). Gastric acid response to pentagastrin and histamine after extragastric vagotomy in dogs. *Gastroenterology*, **59**, 364-371.