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Comparative study of the value of the calcium, secretin, and meal stimulated increase in serum gastrin to the diagnosis of the Zollinger-Ellison syndrome

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SUMMARY To evaluate the usefulness of provocation tests in the diagnosis of the Zollinger-Ellison (ZE) syndrome stimulation tests with calcium, 15 mg/kg.3 h, and secretin GIH, 1 U/kg.30 s, were performed in 15 patients with histologically proven or suspected ZE syndrome. Nine of these 15 patients were without previous gastric surgery and in them meal stimulated serum gastrin levels were measured as well. These tests were also performed in normal subjects and in patients with duodenal ulcer, antrectomy, total gastrectomy, and achlorhydria. All tests were considered to be positive if a more than a 50% increase in serum gastrin was found. The results indicate that secretin stimulation is the provocation test of first choice in the diagnosis of this syndrome. This test is most valuable for the following reasons: (1) there were few (two out of 15) false-negative test results in ZE patients; (2) there were no false-positive tests in 69 patients without gastrinoma; (3) it was easy and quick to perform; and (4) there were no adverse reactions. The two ZE patients with negative secretin stimulation tests had negative calcium provocation tests as well, in spite of histologically proven gastrinoma. In 11 patients with suspected or proven ZE syndrome and basal serum gastrin levels of less than 1000 pg/ml a rather good correlation ($r = 0{\cdot}841$; $P < 0{\cdot}01$) was found between the percental increase in serum gastrin after stimulation by calcium and secretin. Meal stimulated serum gastrin levels are helpful only in patients without previous gastric surgery.

The preoperative diagnosis of Zollinger-Ellison (ZE) syndrome is based on the combination of basal gastric acid hypersecretion and hypergastrinaemia (Isenberg *et al.*, 1973). The criteria of acid secretion as proposed for the ZE syndrome, however, give both false positive and false negative results (Aoyagi and Summerskill, 1966; Kaye *et al.*, 1970; Lewin *et al.*, 1972). The serum gastrin level, as measured by radioimmunoassay, is a valuable tool for the diagnosis of ZE syndrome (Thompson *et al.*, 1972a; Isenberg *et al.*, 1973; Walsh and Grossman, 1975). In some ZE patients, however, the serum gastrin level may at times be only slightly raised and an overlap with non-ZE patients may be present (Thompson *et al.*, 1972a; Isenberg *et al.*, 1973; Walsh and Grossman, 1975). On the other hand, hypergastrinaemia in the absence of achlorhydria or gastrinoma has been found in patients with excluded gastric antrum (Korman *et al.*, 1972b), antral G-cell hyperplasia (Polak *et al.*, 1972; Ganguli *et al.*, 1974), non-tumorous hypergastrinaemic hyperchlorhydria (Straus and Yalow, 1975), uraemia (Korman *et al.*, 1972a), postvagotomy (Stern and Walsh, 1973), pyloric obstruction (Feurle *et al.*, 1972), and postprandial conditions (Berson and Yalow, 1972). Provocation tests have been advocated in patients suspected of ZE syndrome with fasting serum gastrin levels of less than 1000 pg/ml (Isenberg *et al.*, 1973) or less than 10 times the normal median (Walsh and Grossman, 1975). The aim of stimulation tests is to differentiate tumorous from antral gastrin in patients with slight or moderate hypergastrinaemia.

Various provocation tests have been proposed, such as administration of calcium (Passaro *et al.*, 1972), secretin (Isenberg *et al.*, 1972; Thompson *et al.*, 1972b), glucagon (Korman, 1973a; Becker *et al.*, 1973), and ingestion of a protein rich meal

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(Berson and Yalow, 1972). The value of these tests has been studied in small series (Berson and Yalow, 1972; Isenberg *et al.*, 1972; Passaro *et al.*, 1972; Thompson *et al.*, 1972b; Becker *et al.*, 1973; Bradley *et al.*, 1973; Korman *et al.*, 1973a, b; Bonfils *et al.*, 1974) and, recently, in relatively larger groups of ZE patients (Creutzfeldt *et al.*, 1975; Thompson *et al.*, 1975). However, comparison of the value of different provocation tests in the same patient has not been recorded previously.

In this study, the significance of calcium and secretin stimulation tests was determined in 15 patients with histologically proven or suspected ZE syndrome. Moreover, the increases in serum gastrin after both provocation tests were compared. The effect of ingestion of a standard test meal on serum gastrin was studied in nine ZE patients without previous gastric surgery. The incidence of false test results in patients without gastrinoma was evaluated by studying these tests in normal subjects, duodenal ulcer patients, patients with antrectomy and gastroduodenostomy (Billroth I) or gastrojejunostomy (Billroth II), total gastrectomy, and achlorhydria.

Methods

The characteristics of 15 patients with ZE syndrome are summarised in Table 1. The serum gastrin levels recorded in the Table are the lowest and highest values found during follow-up periods from six months to 3½ years. The wide ranges in serum gastrin concentrations in some ZE patients are caused by the effect of progressive tumour growth or surgical procedures, such as total gastrectomy and parathyroidectomy, on the serum gastrin level. The diagnosis of duodenal ulcer and stomal ulcer was made by barium meal or endoscopy. Achlorhydria was defined as a gastric pH of more than 6 after stimulation with pentagastrin in an intramuscular dose of 6 μg/kg.

The calcium stimulation test was performed as described by Passaro *et al.* (1972). After an overnight fast 5 mg/kg.h calcium was infused as calcium gluconate over three hours. Serum gastrin levels before and at the end of the calcium infusion were used for calculation.

After drawing two fasting blood samples, pure natural porcine secretin GIH (Karolinska Institute, Stockholm) in a dose of 1 U/kg was injected intravenously within 30 seconds. Five, 10, and 15 minutes after secretin injection three more blood samples were taken for measurement of serum gastrin levels. Because the gastrin peak was always found at five minutes after secretin injection, the fasting and five minutes' post-secretin gastrin level were used for calculation of the result.

In the meal stimulation test, fasting subjects ingested a standard test meal within 15 minutes. This meal consisted of one slice of bread, 50 g of cheese, one boiled egg, and 200 ml of milk, corresponding to 30 g of protein, 20 g of fat, and 25 g of carbohydrate. Blood samples were drawn before and 15, 30, 45, 60, 90, 120, and 150 minutes after the start of the meal for determination of serum gastrin levels. The fasting and the highest postprandial serum gastrin concentration was used for calculation.

Table 1 *Features of 15 patients with Zollinger-Ellison syndrome*

Patient	*Sex*	*Age (yr)*	*Basal acid output (mmol H^+/h)*	*Serum gastrin (pg/ml)*	*Gastrinoma (tissue diagnosis)*
1	F	42	32·1*	620—960000	+
2	M	39	67·0	400— 1150	−‡
3	F	17	57·5	3100— 21000	+
4	F	49	6·4*	530— 750	−§
5	M	48	40·3	190— 1490	+
6	M	61	35·5	1540— 3280	−§
7	M	43	46·0	215— 320	−†
8	F	70	pH 1·2	400— 1300	+
9	M	26	60·0	530— 850	−†
10	F	64	4·3*	10800— 27100	+
11	F	38	12·5	250— 380	−†
12	F	37	23·4	350— 470	−†
13	F	50	15·4	142— 196	−†
14	M	40	19·2	140— 252	−†
15	F	43	15·1	196— 510	−†
Normal values (mean ± 1 SD)			2·3 ± 2·6 (n = 20)	66 ± 18 (n = 100)	

*After partial gastrectomy.
†No laparotomy.
‡Nodular pancreas; no tissue diagnosis.
§Persistent raised serum gastrin levels after total gastrectomy.

In one ZE patient a secretin stimulation test was performed immediately after three hours' calcium infusion. The result of this test was compared with that of secretin administration under basal conditions in the same patient.

Serum gastrin levels were measured by radioimmunoassay using a rabbit antibody (Rehfeld *et al.*, 1972; Lamers and van Tongeren, 1975). This antibody, raised against human gastrin I covalently coupled to bovine albumin, binds the gastrin components with an almost equimolar potency (Rehfeld *et al.*, 1975). In 100 normal subjects the serum gastrin level was 66 ± 18 pg/ml (mean ± 1 SD).

Calcium, secretin, and meal stimulation tests were considered to be positive if serum gastrin level increased at least 50% of basal value. This criterion has proved to be of value in the differentiation between patients with and without ZE syndrome by calcium infusion (Lamers and van Tongeren, 1976).

Regression analysis was by the method of least squares with calculation of slope, regression coefficient, and intercept.

Results

Calcium infusion led to an increase in serum gastrin in all 15 ZE patients studied (Table 2; Fig. 1). In two patients, however, this test had to be considered negative, because only a slight rise in gastrin was observed.

Intravenous administration of secretin led to a rise in serum gastrin in all 15 ZE patients (Table 2; Fig. 2). In the two patients with a negative calcium provocation test secretin stimulated increase in serum gastrin was also less than 50% of basal value.

In none of the ZE patients was found the combination of a positive calcium test and negative secretin test or a negative calcium test and a positive secretin test.

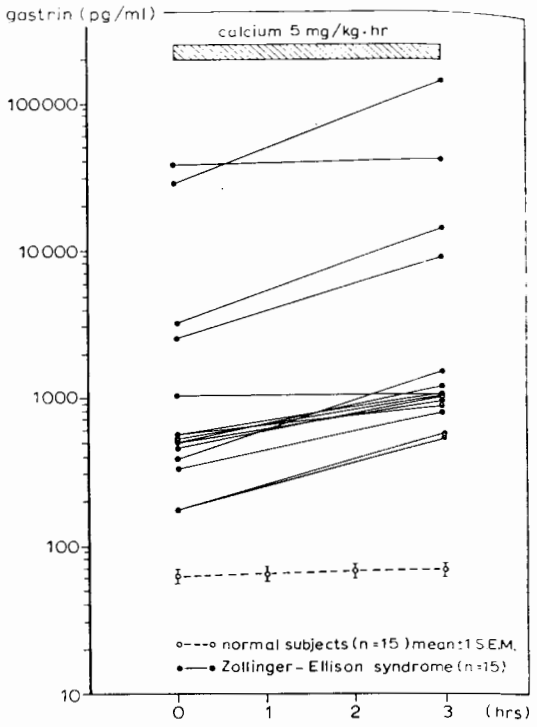

Fig. 1 *Calcium stimulated serum gastrin levels in 15 patients with the Zollinger-Ellison syndrome and 15 normal subjects.*

Table 2 *Calcium, secretin, and meal stimulated increase in serum gastrin in 15 patients with Zollinger-Ellison syndrome*

Patient	*Increase in serum gastrin after stimulation by:*					
	Calcium		*Secretin*		*Meal*	
	pg/ml	*%*	*pg/ml*	*%*	*pg/ml*	*%*
1	500	11	400	16	—	—
2	690	138	870	174	65	10
3	7700	248	19200	480	2800	48
4	330	66	440	57	—	—
5	505	95	565	119	—	—
6	6275	254	4150	205	—	—
7	470	147	170	61	66	21
8	60	6	110	12	—	—
9	400	75	1190	140	760	97
10	80600	340	13300	53	—	—
11	1120	295	660	264	220	42
12	620	177	550	125	132	29
13	404	258	298	211	74	43
14	395	228	357	147	110	44
15	490	96	300	69	180	47
Normal values (mean ± 1 SD)	7 ± 12 (n = 15)	10 ± 18 (n = 15)	4 ± 9 (n = 34)	8 ± 15 (n = 34)	52 ± 28 (n = 12)	99 ± 51 (n = 12)

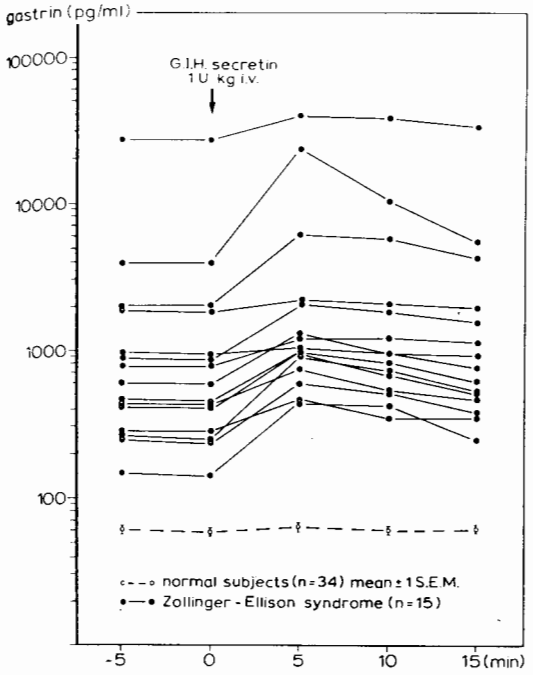

Fig. 2 *Secretin stimulated serum gastrin levels in 15 patients with the Zollinger-Ellison syndrome and 34 normal subjects.*

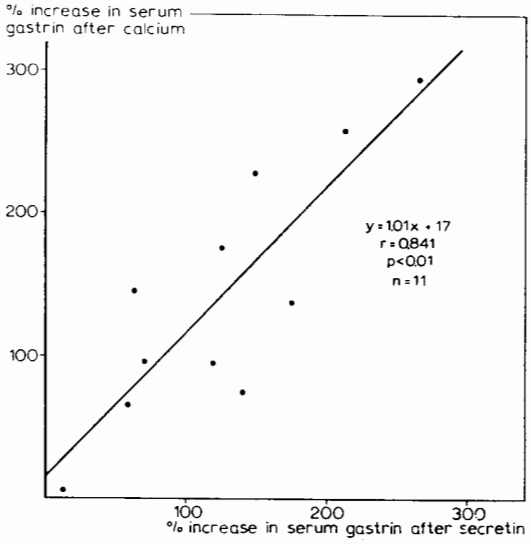

Fig. 3 *Comparison between the percental rises in serum gastrin after stimulation by calcium and secretin in 11 Zollinger-Ellison patients with basal serum gastrin levels of less than 1000 pg/ml.*

The percental increases in serum gastrin after calcium and secretin provocation in 11 ZE patients with basal gastrin levels of less than 1000 pg/ml are compared in Fig. 3. In these patients a good correlation was found between the rises in gastrin after both provocation tests ($r = 0{\cdot}841$; $P < 0{\cdot}01$). In the comparison between the increases in serum gastrin after calcium and secretin in four ZE patients with basal serum gastrin levels of more than 1000 pg/ml, the gastrin response to calcium was found more pronounced in one, almost equal in two, and more marked after secretin in one (Table 2).

One (patient 1) of the two patients with negative calcium and secretin tests had a basal serum gastrin level of more than 1000 pg/ml, whereas the other patient (patient 8) had a fasting serum gastrin concentration of less than 1000 pg/ml at the time of study. The diagnosis of ZE syndrome was histologically proven in these two patients with negative provocation tests.

In one ZE patient the gastrin response to secretin under basal conditions was compared with the increase in serum gastrin after secretin administration at the end of a three hours' calcium infusion test. Calcium infusion led to a rise in serum calcium from 2·4 to 3·5 mmol/l and in serum gastrin from 350 to 970 pg/ml. This calcium test was immediately followed by intravenous administration of 1 U/kg. 30 s secretin GIH. The serum gastrin level rose from 970 up to 2500 pg/ml within five minutes (Fig. 4). When the patient had a secretin stimulation test under basal conditions the serum gastrin level increased from 440 to 990 pg/ml (Fig. 4).

Only one out of nine ZE patients without previous gastric surgery had a positive meal stimulation test, whereas the increase in gastrin in the other eight patients was less than 50% of basal level (Table 2; Fig. 5).

The incidence of false positive calcium and secretin tests and false negative meal tests in patients without ZE syndrome was studied in normal subjects, duodenal ulcer patients, patients with Billroth I and Billroth II antrectomy, total gastrectomy, and achlorhydria (Table 3). A more than 50% increase in serum gastrin after calcium infusion was found in three out of six patients with achlorhydria, but not in the other groups studied. None of the non-ZE patients had a positive secretin provocation test. A post-prandial increase in serum gastrin of less than 50% of basal value was found in three out of 12 normal controls and in two out of nine achlorhydric patients. In patients with antrectomy or total gastrectomy negative meal tests were frequently found: in two out of nine patients with Billroth I antrectomy, in all seven patients with Billroth II antrectomy and

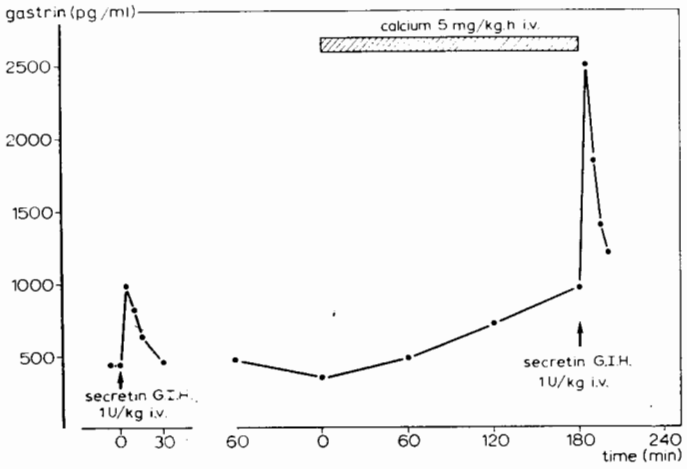

Fig. 4 *Comparison between the secretin stimulated increases in serum gastrin under basal conditions and after three hours' calcium infusion in a patient with the Zollinger-Ellison syndrome. Note the initial fall in serum gastrin during gastric aspiration before the start of the calcium infusion.*

Table 3 *Incidence of positive stimulation tests (defined as increase in serum gastrin of at least 50%) in patients with Zollinger-Ellison syndrome, in normal subjects, and in patients with duodenal ulcer, achlorhydria, Billroth I and Billroth II antrectomy, and total gastrectomy*

	Stimulation test					
	Positive calcium		*Positive secretin*		*Positive meal*	
	(no.)	*(%)*	*(no.)*	*(%)*	*(no.)*	*(%)*
ZE syndrome	13/15	87	13/15	87	1/9	11
Normal subjects	0/15	0	0/34	0	9/12	75
Duodenal ulcer	0/10	0	0/14	0	16/16	100
Achlorhydria	3/6	50	0/11	0	7/9	78
Billroth I antrectomy	0/2	0	0/4	0	7/9	78
Billroth II antrectomy	0/7	0	0/6	0	0/7	0
Total gastrectomy	0/5	0	—	—	0/7	0

in all seven patients with total gastrectomy. All 16 duodenal ulcer patients had a post-prandial increase in serum gastrin of more than 50% of basal value (Table 3.)

Calcium infusion was accompanied by gastric pain, heartburn, nausea, and vomiting in a small number of subjects and phlebitis of a forearm vein in one patient. No adverse reactions were observed after secretin administration or ingestion of the test meal.

Discussion

In this study the value of different provocation tests in distinguishing ZE patients from patients without gastrinoma has been evaluated.

A provocation test is valuable in the diagnosis of ZE syndrome if: (1) the number of false test results in ZE patients is small; (2) the number of false test results in non-ZE patients is small; (3) the test is easy and fast to perform; (4) the test has no or only minor adverse reactions.

PROVISO 1

False negative calcium stimulation tests were found in two out of 15 ZE patients. The secretin stimulation test was also found to be negative in the same two patients with histologically proven gastrinoma.

Different hypotheses have been proposed in the literature to account for these negative stimulation tests in ZE patients, such as a low gastrin content of tumour and metastases (Walsh and Grossman, 1975), the influence of gastrectomy (Bonfils *et al.*, 1974), and—as far as negative secretin tests are concerned—coexisting glucagonoma (Creutzfeldt *et al.*, 1975). However, the exact reason for the negative stimulation tests in ZE patients has so far been obscure. Moreover, the frequency in the literature of negative stimulation tests in ZE patients is difficult to evaluate, because different amounts of provocative agents of different potency over different periods of time have been administered (Lamers *et al.*, 1977).

Provocation tests are considered to be of clinical significance in patients with basal serum gastrin levels of less than 1000 pg/ml (Isenberg *et al.*, 1973). When the percental increases in serum gastrin after stimulation with calcium and secretin are compared in ZE patients with fasting serum gastrin levels of less than 1000 pg/ml the correlation between the results is rather good (see Fig. 3). The slope of 1·01 in Fig. 3 indicates an almost equal potency of calcium and secretin, in the amounts used, to increase serum gastrin levels.

In ZE patients with markedly raised basal gastrin

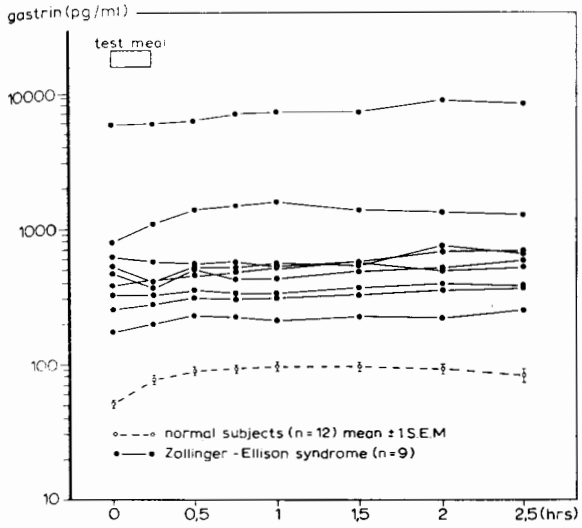

Fig. 5 *Meal stimulated serum gastrin levels in nine patients with the Zollinger-Ellison syndrome without previous gastric surgery and in 12 normal controls.*

levels of more than 1000 pg/ml the correlation between the rise in serum gastrin after both provocative agents was poor. The reason for the different sensitivity of the tumour to the two provocative agents is unclear.

In one ZE patient the rise in serum gastrin after secretin administration was more marked when this test was performed during hypercalcaemia after calcium infusion (see Fig. 4). From these data it may be concluded that the provocative agents are able to potentiate each other. Moreover, it is evident that calcium infusion does not lead to exhaustion of the tumorous gastrin content. Both in acute hypercalcaemia after calcium infusion (see Fig. 4) and in chronic hypercalcaemia, as in coexisting hyperparathyroidism and ZE syndrome, secretin is effective in increasing serum gastrin levels (Lamers *et al.*, 1977). How far calcium or secretin administration stimulates not only the release but also the synthesis of gastrin by the tumour has still to be investigated.

It has been found by Berson and Yalow (1972), that patients with ZE syndrome show no or only minor increases in serum gastrin after ingestion of a protein-rich meal. These results are interpreted by the suggestion that extragastric tumorous gastrin, which forms the bulk of serum gastrin in the ZE syndrome, is not stimulated by ingestion of food (Berson and Yalow, 1972; Isenberg *et al.*, 1973). Only one (patient 9) out of nine ZE patients without previous gastric surgery from this study had an increase in serum gastrin of more than 50% of basal value. Although this patient has not been operated on, the diagnosis of ZE syndrome was verified by the combination of a very high basal gastric acid output, and positive calcium and positive secretin stimulation tests. Patients with non-tumorous hypergastrinaemia of antral origin with hyperchlorhydria have in general a lower basal acid output, negative calcium and secretin stimulation tests and a more pronounced increase in gastrin after a standard test meal in comparison with the results in this patient (Berson and Yalow, 1972; Straus and Yalow, 1975).

Thompson *et al.* (1975) described a post-prandial increase in serum gastrin of less than 50% in both ZE patients without previous gastric surgery studied, whereas Creutzfeldt *et al.* (1975) found a more than 50% increase in gastrin in the two unoperated ZE patients from the series. The reason for the marked increase in serum gastrin after a test meal in some ZE patients is not clear. Several mechanisms may be put forward to account for the pronounced meal stimulated increase in serum gastrin in these patients, as direct interaction between food and a tumour originated in the duodenal wall, the release of a gastrin stimulating agent—for example, secretin—from the small intestine and co-existing antral G-cell hyperplasia and pancreatic tumours (Polak *et al.*, 1972). One of the ZE patients with marked increase in serum gastrin after ingestion of food described by Creutzfeldt *et al.* (1975) has been operated on and a duodenal wall tumour was found. A better understanding of the factors responsible for the food stimulated rise in serum gastrin in some ZE patients is of considerable pathophysiological interest.

PROVISO 2

False positive calcium stimulation tests were found

in three out of six patients with achlorhydria, but in none of the other non-ZE patients. False positive secretin tests were not observed. The secretin test is more valuable than the calcium test because this test differentiates between hypergastrinaemia of antral and tumorous origin. In patients with hypergastrinaemia of antral origin administration of secretin usually leads to a decrease in serum gastrin, as in achlorhydria (Korman *et al.*, 1973b; Lamers *et al.*, 1977), excluded gastric antrum (Korman *et al.*, 1972b), non-tumorous hypergastrinaemic hyperchlorhydria (Straus and Yalow, 1975), and postprandial conditions (Thompson *et al.*, 1972b). In patients with achlorhydria and excluded gastric antrum, marked increases in serum gastrin after calcium infusion have been found (Straus and Yalow, 1975; Lamers and van Tongeren 1976).

Increases in serum gastrin of less than 50% of basal value after a standard test meal were found in patients of all groups without gastrinoma, except for duodenal ulcer patients who all showed marked rises in serum gastrin after ingestion of food. Because the meal stimulated rise in serum gastrin in ZE patients with partial or total gastrectomy is often more than 50% of basal value (Thompson *et al.*, 1972; Creutzfeldt *et al.*, 1975; Thompson *et al.*, 1975) and the increase in gastrectomised patients without gastrinoma is often less than 50% of basal gastrin level, it may be concluded that meal stimulation tests help to differentiate ZE patients from non-ZE patients only in cases without previous gastric surgery.

PROVISO 3

The secretin stimulation test takes only five to 20 minutes, whereas the calcium stimulation test takes three hours and the meal stimulation test 2½ hours. The secretin test is easy to perform because only one intravenous injection and no infusion is needed.

PROVISO 4

The calcium stimulation test was accompanied by moderate complaints in a small group of patients, whereas no untoward reactions to secretin or to the standard test meal were observed. Because of the risk of complications as a result of the long-standing calcium stimulated gastric acid secretion, gastric aspiration may be needed in ZE patients during and after the calcium infusion. Moreover, the calcium load may be dangerous in elderly patients and in patients with pre-existing hypercalcaemia.

It can be concluded from this study that the secretin stimulation test should be recommended as provocation test of first choice in equivocal cases of ZE syndrome.

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References

Aoyagi, T., and Summerskill, W. H. J. (1966). Gastric secretion with ulcerogenic islet cell tumor. *Archives of Internal Medicine*, **117**, 667-672.

Becker, H. D., Reeder, D. D., and Thompson, J. C. (1973). Effect of glucagon on circulating gastrin. *Gastroenterology*, **65**, 28-35.

Berson, S. A., and Yalow, R. S. (1972). Radioimmunoassay in gastroenterology, *Gastroenterology*, **62**, 1061-1084.

Bonfils, S., Mignon, M., and Accary, J. P. (1974). The secretin provocation test in the diagnosis of Zollinger-Ellison syndrome. *Gut*, **15**, 841.

Bradley, E. L., Galambos, J. T., Lobley, C. R., and Chan, Y-K. (1973). Secretin-gastrin relationships in Zollinger-Ellison syndrome. *Surgery*, **73**, 550-556.

Creutzfeldt, W., Arnold, R., Creutzfeldt, C., and Track, N. S. (1975). Pathomorphologic, biochemical, and diagnostic aspects of gastrinomas (Zollinger-Ellison syndrome). *Human Pathology*, **6**, 47-76.

Feurle, G., Ketterer, H., Becker, H. D., and Creutzfeldt, W. (1972). Circidian serum gastrin concentrations in control persons and in patients with ulcer disease. *Scandinavian Journal of Gastroenterology*, **7**, 177-183.

Ganguli, P. C., Polak, J. M., Pearse, A. G. E., Elder, J. B., and Hegarty, M. (1974). Antral-gastrin-cell hyperplasia in peptic-ulcer disease. *Lancet*, **1**, 583-586.

Isenberg, J. I., Walsh, J. H., and Grossman, M. I. (1973). Zollinger-Ellison syndrome. *Gastroenterology*, **65**, 140-165.

Isenberg, J. I., Walsh, J. H., Passaro, E., Moore, E. W., and Grossman, M. I. (1972). Unusual effect of secretin on serum gastrin, serum calcium, and gastric acid secretion in a patient with suspected Zollinger-Ellison syndrome. *Gastroenterology*, **62**, 626-631.

Kaye, M. D., Rhodes, J., and Beck, P. (1970). Gastric secretion in duodenal ulcer, with particular reference to the diagnosis of Zollinger-Ellison syndrome. *Gastroenterology*, **58**, 476-481.

Korman, M. G., Laver, M. C., and Hansky, J. (1972a). Hypergastrinaemia in chronic renal failure. *British Medical Journal*, **1**, 209-210.

Korman, M. G., Scott, D. F., Hansky, J., and Wilson, H. (1972b). Hypergastrinaemia due to an excluded gastric antrum; a proposed method for differentiation from Zollinger-Ellison syndrome. *Australian and New Zealand Journal of Medicine*, **3**, 266-271.

Korman, M. G., Soveny, C., and Hansky, J. (1973a). The effect of glucagon on serum gastrin. II. Studies in pernicious anaemia and the Zollinger-Ellison syndrome. *Gut*, **14**, 459-461.

Korman, M. G., Soveny, C., and Hansky, J. (1973b). Paradoxical effect of secretin on serum immunoreactive gastrin in the Zollinger-Ellison syndrome. *Digestion*, **8**, 407-416.

Lamers, C. B. H., and van Tongeren, J. H. M. (1975). De klinische betekenis van de gastrinebepaling in het serum. *Nederlands Tijdschrift voor Geneeskunde*, **119**, 2024-2031.

Lamers, C. B. H., and van Tongeren, J. H. M. (1976).

Serum gastrin response to acute and chronic hypercalcemia. *Netherlands Journal of Medicine*, **19**, 159.

Lamers, C. B., Buis, J. T., and van Tongeren, J. H. (1977). Secretin stimulated serum gastrin levels in patients with hyperparathyroidism from families with multiple endocrine adenomatosis type I. *Annals of Internal Medicine* (In press).

Lewin, M. R., Stagg, B. H., and Clark, C. G. (1972). Acid secretion, plasma gastrin levels and the diagnosis of the Zollinger-Ellison syndrome. *Gut*, **13**, 849.

Passaro, E., Basso, N., and Walsh, J. H. (1972). Calcium challenge in the Zollinger-Ellison syndrome. *Surgery*, **72**, 60-67.

Polak, J. M., Stagg, B., and Pearse, A. G. E. (1972). Two types of Zollinger-Ellison syndrome: immunofluorescent, cytochemical and ultrastructural studies of the antral and pancreatic gastrin cells in different clinical states. *Gut*, **13**, 501-512.

Rehfeld, J. F., Stadil, F., and Rubin, B. (1972). Production and evaluation of antibodies for the radioimmunoassay of gastrin. *Scandinavian Journal of Clinical and Laboratory Investigation*, **30**, 221-232.

Rehfeld, J. F., Stadil, F., Malmstrøm, J., and Miyata, M. (1975). Gastrin heterogeneity in serum and tissue. In *Gastrointestinal Hormones*, p. 43. Edited by J. C. Thompson. University of Texas Press: Austin.

Stern, D. H., and Walsh, J. H. (1973). Gastrin release in postoperative ulcer patients: evidence for release of duodenal gastrin. *Gastroenterology*, **64**, 363-369.

Straus, E., and Yalow, R. S. (1975). Differential diagnosis of hypergastrinemia. In *Gastrointestinal Hormones*, p. 99. Edited by J. C. Thompson. University of Texas Press: Austin.

Thompson, J. C., Reeder, D. D., and Bunchman, H. H. (1972a). Clinical role of serum gastrin measurements in the Zollinger-Ellison syndrome. *American Journal of Surgery*, **124**, 250-260.

Thompson, J. C., Reeder, D. D., Bunchman, H. H., Becker, H. D., and Brandt, E. N. (1972b). Effect of secretin on circulating gastrin. *Annals of Surgery*, **176**, 384-393.

Thompson, J. C., Reeder, D. D., Villar, H. V., and Roberts Fender, H. (1975). Natural history and experience with diagnosis and treatment of the Zollinger-Ellison syndrome. *Surgery, Gynecology and Obstetrics*, **140**, 721-739.

Walsh, J. H., and Grossman, M. I. (1975). Gastrin (second of two parts). *New England Journal of Medicine*, **292**, 1377-1384.