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Serum gastrin in Zollinger-Ellison syndrome: II. Prospective study of gastrin provocative testing in 293 NIH patients and comparison with 537 cases from the literature. Evaluation of diagnostic criteria, proposal of new criteria and correlations with clinical and tumoral features

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Abstract

In two-thirds of patients with Zollinger-Ellison syndrome (ZES), fasting serum gastrin (FSG) levels overlap with values seen in other conditions. In these patients, gastrin provocative tests are needed to establish the diagnosis of ZES. Whereas numerous gastrin provocative tests have been proposed, only the secretin, calcium and meal tests are widely used today. Many studies have analyzed gastrin provocative test results in ZES, but they are limited by small patient numbers and methodological differences. To address this issue, we report the results of a prospective National Institutes of Health (NIH) study of gastrin provocative tests in 293 ZES patients and compare these data with those from 537 ZES and 462 non-ZES patients from the literature. In 97–99% of gastrinoma patients an increase in serum gastrin post secretin or post calcium occurred. In NIH ZES patients with <10-fold increase in FSG, the sensitivity/specificity of the widely used criteria were: Δ secretin ≥200 pg/ml (83%/100%), Δ secretin >50% (86%/93%), Δ calcium ≥395 pg/ml (54%/100%) and Δ calcium >50% (78%/83%). A systematic analysis of the sensitivity and specificity of other possible criteria for a positive secretin or calcium test allowed us to identify a new criterion for secretin testing (Δ≥120 pg/ml) with the highest sensitivity/specificity (94%/100%) and to confirm the commonly used criterion for calcium tests (Δ≥395 pg/ml) (62%/100%). This analysis further showed that the secretin test was more sensitive than the calcium test (94% vs. 62%). Our results suggest that secretin stimulation should be used as first-line provocative test because of its greater sensitivity, simplicity and lack of side effects. In ZES patients with a negative secretin test, 38–50% have a positive calcium test. Therefore the calcium test should be considered in patients with a strong clinical suspicion of ZES but a negative secretin test.

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Furthermore, we found that some clinical (diarrhea, duration of medical treatment), laboratory (BAO) and tumoral (size, extent) characteristics correlate with the serum gastrin increase post secretin and post calcium. However, using the proposed criteria, the result of these provocative tests (i.e. positive or negative) is minimally influenced by these factors. Therefore, secretin and calcium provocative tests are reliable in patients with different clinical, laboratory and tumor characteristics. A systematic analysis of meal testing showed that 54–77% of ZES patients have a <50% postprandial serum gastrin increase. However, 9–20% of ZES patients had a >100% increase post meal, causing significant overlap with antral syndromes. Furthermore, we could not confirm the usefulness of meal tests for localization of duodenal gastrinomas. We conclude that the secretin test is a crucial element in the diagnosis of most ZES patients, the calcium test may be useful in selected patients, but our data suggest that the meal test is not helpful in the management of ZES. For secretin testing, the criterion with the highest sensitivity and specificity is an increase of ≥120 pg/ml, which should replace other criteria commonly used today.

Introduction

In the accompanying paper [30], we analyzed the role of fasting serum gastrin (FSG) and confirmed its importance in providing relevant information for diagnosis and management of ZES. However, like others [39,80,136,140,168,184,196,199,201,205,247,266,306,341,343,380], we found in the majority of patients, the determination of FSG, alone or in combination with acid secretion studies, cannot establish the diagnosis of ZES [30]. In these patients, gastrin provocative tests are needed. Of the several tests developed, only secretin, calcium and meal stimulation are widely used in the today [78,110,111,165,165,167,196,219,238,250,397]. However, the exact role of these provocative tests, the optimal testing procedures and criteria for positive responses remain controversial, so that some studies even question their overall usefulness [304,343,344]. This has occurred because most existing studies have one or multiple limitations including small patient numbers, retrospective nature, non-standardized radioimmunoassay (RIA), different criteria for positivity, different testing procedures and lack of stratification for FSG < or > 10x normal[110,120,152,165,167,196,248,249,295,344,360,381,397].

To address these issues, we analyzed the results of secretin, calcium and meal provocative tests in 293 ZES patients from a 31-year prospective NIH study. FSG was determined using well-established gastrin RIAs [30]. Provocative tests were performed using well-established time points and standardized stimulant conditions [110,111]. Because of the prospective nature of our study with regular follow-ups, including detailed imaging studies and surgical exploration [121,279,283,319,320,349], correlations of test results with clinical, laboratory and tumoral parameters were possible. We compared our data to results from 537 ZES patients from the literature. Furthermore, we determined the specificity of provocative tests by analyzing data from published non-ZES patients. This approach allowed us to determine the optimal criteria for positive secretin and calcium tests and to propose a new criterion for the secretin test with high sensitivity/specificity. In conjunction with the accompanying report [30], this extensive analysis allowed us to identify important guidelines for gastrin provocative tests in the clinical management of ZES patients.

Case History

The detailed history and clinical findings of this 38-year-old man with a 12-year history of recurrent upper gastrointestinal symptoms resistant to standard medical treatment are reported in the accompanying paper [30]. The patient was hospitalized for an acute abdomen requiring surgical exploration for a perforated duodenal ulcer with an oversew as well as a vagotomy/pyloroplasty. His FSG was 221 pg/ml (normal <100) while taking omeprazole and he had an elevated serum calcium (2.41 mM, normal 2.05–2.50 mM). The possibility of ZES was raised and because no secretin was available, a calcium infusion study was performed. The calcium test results supported the diagnosis with his FSG increasing from 215 pg/ml to 1010 pg/ml after 180 minutes (Figure 1, middle panel). Subsequently, the patient was referred to the NIH where FSG levels were 200–250 pg/ml (normal <100) and basal acid output (BAO) was 9 mEq/hr 2 weeks after stopping omeprazole. A secretin test with 2-unit/kg bolus of GIH secretin showed an increase from 217 to 1150 pg/ml (Figure 1, left panel) and a meal test showed an increase of only 30% over basal (Figure 1, right panel), supporting the diagnosis of ZES. Imaging revealed three pancreatic lesions while further biochemical studies showed hyperparathyroidism and MEN1 (see accompanying paper, Figure 1[30]). A parathyroidectomy was performed, followed by an abdominal exploration with resection of pancreatic/duodenal tumors and metastatic tumor in lymph nodes. Postoperatively, the secretin test was negative (i.e. <200 pg/ml increase) [110,238,397], but after three years became positive. The patient has remained asymptomatic with no evidence of recurrent tumor on imaging studies, however, the secretin test has remained positive.

Comment:

This case illustrates the difficulty in making the diagnosis of ZES with the increasing use of potent acid suppressants such as proton pump inhibitors (PPI's). Therefore, the correct assessment of FSG and gastrin provocative tests have become essential in the diagnosis of ZES [67,144,160,231,244,257]. In this patient, the diagnosis was complicated because of an initial FSG elevation of only 2-fold (characteristically increased >10-fold in 40–60% of ZES patients) [110,111,162,165,250]. Furthermore, this moderate hypergastrinemia was detected while the patient was taking omeprazole, which can cause FSG elevations in patients without ZES [67,80,156,187] and the BAO was only moderately increased to 9 mEq/hr (mean 16–26 mEq/hr post gastric surgery in ZES patients)[160,165,250,315,319]. This case illustrates the importance of the secretin test in the diagnosis of ZES and shows that PPI's should be discontinued prior to FSG determination. As false positive secretin tests have been reported in achlorhydric patients [98,141,219], gastrin provocative testing may not be reliable in patients treated with PPI's, providing another reason PPI's should be carefully stopped to determine the diagnosis of ZES. Lastly, this case illustrates the importance of assessing both the secretin test and the FSG level to determine cure [102,283,284]. This patient underwent a gastrinoma resection and a parathyroidectomy, both of which can affect the FSG [29,72,123,143,157,159,197,234,263,276,281], and subsequently his FSG levels became normal. However, with time, although the FSG level remained normal, the secretin test became positive showing persistent ZES. This latter finding illustrates the particular importance of secretin testing in MEN1 patients post resection or post parathyroidectomy. Numerous patients with MEN1/ZES in the literature

have been reported cured long-term. However, recent studies in MEN/1 ZES patients who underwent repetitive secretin testing show that the long-term cure rate is very low in this patient group (i.e. <1–2%) [210,274,283,286,333].

MATERIALS AND METHODS

All patients admitted to the National Institutes of Health (NIH) with a diagnosis of ZES over a 31-year period (1974–2005) who agreed to participate in the initial and follow-up evaluations were eligible for this study. Details on study organization, diagnostic criteria for ZES or MEN1 and the FSG determination have been described in the accompanying study [30] and the literature [15,16,117,123,220,224,283,320].

FSG levels were determined as described previously [21,30,56,102,110,319]. All gastrin provocative tests were performed prior to any gastrinoma treatment in patients with diffuse metastases who subsequently underwent chemotherapy [379], treatment with α-interferon [298] or somatostatin analogues [334]. FSG and provocative tests were performed prior to gastrinoma resection in all but 13 patients and were usually performed on the initial NIH admission. Furthermore, because correction of hypercalcemia by parathyroidectomy can affect both the FSG level and gastrin provocative test results [72,123,143,157,159,197,234,263,276], all patients with ZES and MEN1 had provocative testing performed prior to any treatment for hyperparathyroidism.

FSG determinations after stimulation with secretin were carried out in all patients, whereas calcium and standard meal tests were carried out routinely until 1995. Results of serum gastrin responses after stimulation were expressed as the relative rise over the pre-test value ($\Delta\% = \frac{\text{gastrin max} - \text{FSG}}{\text{FSD}} \times 100$), or the absolute increase expressed in pg/ml (Δ=gastrin max-FSG). For some criteria, the maximal FSG level after provocative stimulation was considered.

Secretin testing was performed using an intravenous bolus injection (2 U/kg body weight) of Secretin-Kabi (Ferring AB, Malmo, Sweden) [110]. FSG concentrations were measured at −15, −5 and 0 minutes before as well as 2, 5, 10, 15, 20 and 30 minutes after secretin injection. Secretin test results were analyzed using the criterion of McGuigan and Wolfe [110,238] (Δ≥200 pg/ml); the criterion of Deveney and colleagues [78] (Δ≥110 pg/ml); another criterion of Deveney [77] (Δ>100 pg/ml); the criterion of Lamers and van Tongeren [196] (Δ>50%); the criterion of Modlin and colleagues [260] (Δ≥100%); the criterion of Malageleda [219], ($\text{gastrin}_{\text{max}} \geq 335$ pg/ml); and one of the criteria proposed by Poynard and Bonfils [301] ($\text{gastrin}_{\text{max}} \geq 186$ pg/ml).

The calcium infusion provocative test was performed as described previously [78,110] with calcium gluconate (10%) (5 mg calcium/kg per hr)(54 mg/kg per hr of calcium gluconate) given by intravenous infusion for 3 hours. FSG and calcium levels were measured simultaneously at 30 or 15 min before, immediate prior to as well as at 30, 60, 90, 120, 150 and 180 minutes after the calcium infusion. A rise in serum calcium ≥1.5 mEq/l was required for the test to be considered valid. Patients with hypercalcemia, renal disease, cardiac disease or unstable clinical condition did not undergo calcium testing. Calcium test

results were analyzed using the criterion of Deveney [78], (Δ≥395 pg/ml); a second criterion of Deveney [77] (Δ>450 pg/ml); the criterion of Lamers and van Tongeren [196] (Δ>50%); the criterion proposed by Modlin and colleagues [260] (Δ≥100%); and the criterion of Malageleda [219], ($gastrin_{max}$≥326 pg/ml).

The standard meal test was performed as described previously [111] and consisted of 30 g of protein, 20 g of fat and 25 g of carbohydrate [111,196]. FSG levels were measured at −15, 0, 30, 60, 90 and 120 min [111]. Test results were analyzed using the criterion of Lamers and van Tongeren [196] (Δ>50%) and the criterion of Malageleda [219] ($gastrin_{max}$≥500 pg/ml). Meal tests were not performed if the patient had a prior total gastrectomy or if they could not take oral feedings.

Basal acid output (BAO), maximal acid output (MAO) and assessment of acid secretory control by anti-secretory medication were measured [30,223,225,228,245,310,319,355]. Patient histories [30,123,320,409], laboratory investigations [30,117,319,320], endoscopy [30,36,122,320] and imaging studies using both conventional [109,206,227,292,297,332,353,354,382] and functional[56,85,185,256,288,357] localization methods were performed. Based on the imaging studies and surgical exploration, patients were stratified into those with primary tumor only, with lymph node metastases and those with liver metastases. Lymph node and liver metastases were established by biopsy in all patients [350,384,409].

Surgical exploration was performed in all patients with ZES without MEN1, without diffuse liver metastases or an illness limiting life-expectancy and in patients with MEN1 with imageable lesions >2.5 cm as described previously [3,30,103,104,112,273,275,277,279,280,282,286,287,349,387]. Patients with limited hepatic metastases considered resectable also underwent surgical exploration and resection [52,274,278,289,290,387]. For the purpose of analysis of the effect of primary tumor location, patients were divided into those who had only a duodenal primary; a pancreatic primary; a lymph node primary; a primary in another non-duodenal, non-pancreatic, non-lymph node location; or a primary tumor in an unknown location. A primary tumor of the lymph node was defined as occurring in a patient who was disease-free [normal fasting gastrin, negative provocative test and negative imaging [102]] post-resection of only a lymph node gastrinoma as described previously [14,273,283]. Other non-duodenal-pancreatic-lymph node primary locations were defined as occurring in patients who were disease-free post resection of a gastrinoma from these sites [283,402,403].

Computed tomography or an MRI of the sella turcica and determinations of serum prolactin, calcium (total and ionized) and parathyroid hormone concentrations (using both an assay for the intact PTH molecule and with an antibody directed against the mid-portion of PTH) were also performed to determine if associated MEN1 was present as described previously [16,29,123,283].

Literature review of fasting serum gastrin and provocative tests in patients with ZES and in non-ZES control patients.

To compare our results to previously reported data, we attempted to identify all published cases of ZES with gastrin provocative test data. MEDLINE search and analysis was

performed as described in the accompanying paper [30]. For the provocative tests, the percent rise of FSG above baseline, Δ (%), and the absolute increase in FSG above baseline, Δ (pg/ml), were calculated. Maximal FSG values after provocative tests were normalized for the highest normal value used in each publication. Furthermore, we collected published data on secretin tests in non-ZES patients with and without achlorhydria. Only the secretin test results from literature patients treated with synthetic or GIH secretin were analyzed, not Boot's secretin, because it can cause false positive responses and is no longer available [40,43,128,238,265,302,398]. Furthermore, only secretin results from literature ZES patients in whom the secretin test was performed using an intravenous bolus administration of a dose equivalent to 2 units per kg body weight of secretin were used for comparison to the NIH results. Results of literature patients tested with 1 unit per kg, 75 total units or ≥3 units per kg were analyzed separately to determine the effect of secretin dose. Results from calcium testing in ZES and non-ZES patients were only included if the calcium test was performed with a calcium infusion over 3 hours using 5 mg calcium per kg per hour.

Statistical analysis

Statistical analysis was performed using the Student t test for unpaired values, the Mann-Whitney-U test, the Fisher's exact test and the Chi-squared test using the computer programs Statview (SAS Institute, Casy, NC) and Statistica MAC (Statsoft, Tulsa, OK). *P* values <0.05 were considered significant. All continuous variables with a normal distribution are reported as mean ± SEM, otherwise the median is indicated. Regression lines were calculated using a least-squares analysis.

Results

General characteristics of NIH and literature ZES patients (Table 1)

Gastrin provocative test results from 293 NIH and 537 literature ZES patients were analyzed and their clinical/laboratory/tumor characteristics compared (Table 1). In agreement with most large series [49,60,92,96,171,253,312,320,339,343,360,383], 29% of NIH patients had ZES with MEN1. This was significantly higher (p=0.017) than 21% of literature ZES patients. Similar to most large series of ZES patients [320], there was a slight male predominance both in the NIH and literature patients. Acid hypersecretion, which is a constant feature of ZES [11,164,166,199,217,240,248–251,315,319,323,343,360,377,383,391], was higher in NIH than in literature patients (Table 1). Increased maximal acid output, which is another characteristic feature of ZES [165,320], was elevated in both groups. Hypergastrinemia, a recognized constant feature of ZES [161,164,166,250], was significantly more pronounced in NIH than in literature patients (median 6.4-fold vs. 4.8-fold increase). The median FSG increase after secretin or calcium (150%) and after a standard meal (33%) was similar in NIH and literature patients (Table 1). In accordance with most recent series [142,145,166,275,279,283,285,286,356], duodenal gastrinomas were more frequent than pancreatic gastrinomas among NIH patients (Table 1). This was not true for literature patients, possibly reflecting the fact that in most early series, the duodenum was not systematically explored at surgery [275,279,280,285,363]. In both the NIH and literature groups, primary gastrinomas occurred in 12% of patients in non-duodenal/non-pancreatic locations (Table 1), including lymph nodes and some rare extra-abdominal locations [1,118,160,166,226,270,339]. Similar to most series [160,166,339], in one

third of patients, the site of the primary was not established. In accordance with recent studies, < 50% of patients had distant metastases and one-third had local lymph node metastases [14,160,166,273,283,286]. In contrast to studies of 1960–1980 [60,92,319,320,347,360,383], prior gastric acid-reducing surgery occurred in <20% of patients, while in most patients, gastric hypersecretion was controlled either with histamine H_2-receptor antagonists or PPI's [49,60,63,92,119,160,161,163,166,383,397].

In accordance with previous studies [110,143,159] sporadic and MEN1/ZES patients had comparable FSG levels (642 vs. 748 pg/ml) and FSG levels after secretin (1513 vs. 2192 pg/ml) or calcium (1550 vs. 2895 pg/ml). However, sporadic ZES patients had significantly lower postprandial gastrin values (810 vs. 1550 pg/ml, $p<0.05$).

Results of gastrin provocative tests in NIH and literature patients (Tables 2 and 3)

To differentiate ZES from other conditions causing hypergastrinemia, various gastrin provocative tests have been developed. Today, the most commonly used are the secretin, calcium and meal tests [40,78,110,111,153,164–167,189,196,238,243,247,295,397]. In previous studies, small number of ZES cases, different methodologies and failure to consider separately patients with FSG<10-fold and >10-fold increased have led to controversy about the role of gastrin provocative tests in ZES [110,304,343,344]. It is especially important to consider separately patients with FSG< and >10-fold increased because the combination of FSG >10-fold increased and hyperchlorhydria (preferably pH<2) is generally considered to be pathognomonic of ZES [40,119,142,248,250,319,360,381,397]. Therefore, in the present study, both the NIH and literature patients were stratified into those with FSG<10 fold or ≥10-fold increased.

The provocative test results (secretin, calcium, meal) were similar in NIH and literature ZES patients (Table 2). In particular, no change or a decrease in FSG levels after secretin or calcium were exceptional, occurring in < 2% of NIH and literature patients (Table 2). The median FSG increase after secretin was similar in NIH and literature patients (i.e. 744 and 600 pg/ml, Table 1), as was the median change after calcium (850 and 994 pg/ml, Table 1). In both groups, few patients (2–7%) had an absolute increase in FSG ≤100 pg/ml or ≤200 (5–8%). The distribution of FSG levels was also generally similar in the NIH and literature ZES patients (Table 3, top). Because only 25–35% of NIH or literature ZES patients have a FSG ≥ 10 fold increased (Table 3), our results confirm that approximately two-thirds of all FSG levels in ZES fall into a non-diagnostic range (i.e. <10 fold increased with acidic gastric pH). Therefore, these FSG values will overlap with those seen in other conditions with hypergastrinemia/hyperchlorhydria (i.e. H. pylori infection, antral G cell hyperplasia/hyperfunction, renal failure, post small bowel resection, gastric antral obstruction [7,9,158,165,167,204,246,250,397]) and gastrin provocative tests are needed.

Numerous criteria have been proposed for a positive gastrin provocative test. The most widely used secretin test criterion, (Δ ≥200 pg/ml), is derived from a review of 14 original studies by McGuigan and Wolfe [238]. In these studies, different secretin preparations (GIH, Boots), doses and modes of administration (bolus, infusion) were used. The Δ ≥200 pg/ml criterion was selected because it allowed the diagnosis of a maximal number of ZES patients without false positives. In that review, this criterion was reported to have a sensitivity of

100% when 2 units/kg bolus injection of secretin was performed. However, we found it to be less sensitive, with 87% of all NIH and 88% of all literature patients having a positive secretin test (Table 3). The sensitivity decreased even further to 83% for the NIH and 87% for the literature ZES patients when the clinically relevant group of patients with FSG <10-fold increased were considered (Table 3).

Deveney proposed Δ secretin≥110 pg/ml and Δ calcium>395 pg/ml had the greatest discriminatory value [78]. When applied to our populations, 93% of all NIH patients and 96% of all literature patients had a positive secretin test, whereas 67% of all NIH and 75% of all literature patients had a positive calcium test. The secretin test's sensitivity remained unchanged in patients with FSG<10-fold increased, whereas the calcium test sensitivity decreased to 54 and 70%. In another publication [77], the authors proposed slightly different criteria (Δ secretin>100 pg/ml, Δ calcium≥450 pg/ml), which lead to comparable results in our study (Table 3).

Lamers and van Tongeren [196] proposed FSG increases >50% for the secretin and calcium test and <50% for the meal were characteristic of ZES. In our study, 84% of all NIH and 81% of all literature patients had a positive secretin test, 79 and 90% had a positive calcium test and 57 and 67%, respectively, had a positive meal test (Table 3). These percentages decreased slightly when only patients with a <10-fold FSG increase were considered (Table 3). However, 20% of all NIH and 15% of all literature ZES patients had a ≥100% increase post meal, a value considered characteristic of antral G-cell hyperplasia [7,9,108,158,167,204,336,347]. In patients with FSG<10-fold increased, it was 19%/9%, respectively (Tables 2, 3).

Malagelada et al. [219] proposed criteria on the basis of the highest FSG value after stimulation. In their study, the authors used maximal FSG levels post provocation of 335 pg/ml, 326 pg/ml and 500 pg/ml for secretin, calcium and meal tests, respectively. In our study, 93% of all NIH and 97% of all literature patients had a positive secretin test, 97% and 92% had a positive calcium test and 74% and 68%, respectively, had a positive meal test (Table 3). These percentages decreased slightly in patients with a <10-fold FSG increase (Table 3).

Modlin et al. [260] proposed a FSG increase >100% post secretin or calcium to diagnose ZES. In our study, 63% of all NIH and 57% of literature patients had a positive secretin test, whereas 57 and 75%, respectively, had a positive calcium test (Table 3). These percentages did not change significantly in patients with FSG<10-fold increased were considered (Table 3).

Poynard and Bonfils [301] proposed that a combination of 4 criteria gave the best sensitivity and specificity with the best single criterion being a maximal FSG after secretin ≥186 pg/ml. With these criteria, 100% of NIH and 99% of literature patients had a positive secretin test and these percentages were identical in patients with a <10-fold FSG increase (Table 3).

In both the NIH and the literature ZES patients, the criterion of an increase of either 110 or 100 pg/ml post secretin had a greater sensitivity than the criterion of a 200 pg/ml increase ($p<0.003$).

Correlation of FSG and serum gastrin increase after gastrin provocative tests (Figure 2)

To investigate the influence of FSG levels on provocative testing, we correlated the FSG and the absolute increase in FSG after secretin (Δ secretin), calcium (Δ calcium) and a meal (Δ meal) in NIH and literature patients. The magnitude of the FSG correlated well with Δ secretin (Figure 2, top panel) and Δ calcium (Figure 2, middle panel) in NIH and literature patients, whereas there was no correlation with Δ meal (Figure 2, bottom panel).

To analyze if these correlations still exist after correction for higher FSG values, we correlated the relative increase in serum gastrin after secretin or calcium with FSG levels and found no significant correlation (r=[−0.068] [−0.18], data not shown), suggesting that the magnitude of the FSG contributes to the higher Δ response but is not associated with a proportional gastrin release post stimulation.

Influence of clinical and laboratory variables on gastrin provocative tests in NIH and literature ZES patients (Tables 4–7, Figure 3)

To determine whether clinical or laboratory variables might influence gastrin provocative testing, these variables were correlated with the increase in FSG levels after stimulation. In NIH patients, extensive data was available allowing a detailed analysis (Table 4), while the effect of only selective variables could be be compared in literature patients (Tables 5–7).

In the NIH patients, age, race, MEN1 status, disease duration, prior treatment with PPI's, the presence/absence of most common ZES symptoms (pain, heartburn) or the presence/absence of manifestations of severe disease (confirmed ulcer, esophageal disease, pyloric obstruction) did not effect secretin or calcium provocative testing (Tables 4, 5, 6). In contrast, higher Δ secretin and Δ calcium levels were seen with female gender and high BAO's, whereas higher Δ secretin levels only were seen in the presence of diarrhea or with a long duration of antisecretory drug treatment. Correlation of clinical or laboratory parameters with the literature data did not demonstrate a relationship between higher Δ secretin or Δ calcium values with higher BAO's or gender (Tables 5, 6, Figure 3). Similar to NIH patients, no relationship with age, MEN1 status or prior gastric-acid reducing surgery was seen (Tables 5, 6). In contrast to the Δ secretin and Δ calcium results in NIH ZES patients, higher Δ meal levels were present in younger patients, patients with a longer disease history, patients with heartburn as an initial symptom (data not shown) or with severe esophageal disease (stricture/dysphagia) and the presence of MEN1, but not with BAO or MAO levels (Tables 4, 7, Figure 3). In the literature ZES patients, no correlations were seen with the Δ meal value and acid secretory levels or clinical parameters (Table 7, Figure 3).

Influence of tumoral variables on provocative test results in NIH and literature ZES patients (Tables 4–7, Figures 3, 4)

In general, primary tumor location had no effect on the Δ secretin or Δ calcium levels in NIH or literature ZES patients (Tables 4–6). Tumor size was associated with an increased Δ secretin and Δ calcium response (Tables 4–6 and Figures 3, 4) in NIH patients more than in the literature ZES patients.

In contrast to secretin and calcium tests, the meal test was not influenced by tumor size in the NIH ZES patients. However, in NIH patients only, a duodenal tumor was associated with a higher Δ meal response, whereas the presence of liver metastases was associated with a lower meal response (Tables 4, 7).

To further investigate the relationship between tumor size/disease extent and secretin provocative testing, we correlated the size of the largest tumor and the primary tumor size with Δ secretin in NIH ZES patients (Figure 4). In the literature patients, only primary tumor size was available for this analysis (Figure 4, lower panel). In NIH ZES patients, there was a significant correlation between the largest tumor size and Δ secretin in all patients and this correlation was even stronger in patients without liver metastases (Figure 4, top panel). No correlation existed with primary tumor size in the NIH patients with or without liver metastases (Figure 4, middle panel). However, in literature ZES patients, a weakly positive correlation between primary tumor size and Δ secretin existed in all patients, which increased in significance in patients without liver metastases (Figure 4, lower panel).

Correlation between various provocative test results in NIH and literature ZES patients (Figure 5)

As secretin and calcium provocative tests were influenced by comparable factors, we further studied the correlation between these different tests. We found a close correlation between Δ secretin and Δ calcium both in NIH and literature patients (Figure 5, top panel). This correlation remained unchanged if relative increases (% increase) post secretin and post calcium were correlated (data not shown). However, there was no correlation or a weak correlation between Δ secretin and Δ meal or Δ calcium and Δ meal in any patient group (Figure 5, middle and bottom panel).

Influence of different variables on the positivity of the various provocative tests in NIH and literature ZES patients (Table 8)

To analyze whether clinical, laboratory or tumor variables could also influence provocative test results, i.e. positive or negative, we investigated the effect of the presence or absence of these variables on the positivity of secretin (Table 8), calcium (data not shown) or meal test (data not shown). In general, there was little concordance between those variables and the positivity of the secretin test in NIH or literature ZES patients (Table 8). This might partially be due to the small numbers of patients in some of the variable groups. The only variable associated with a positive secretin test in both the NIH and literature patients was the presence of a large primary tumor (Table 8). In contrast, only in the NIH ZES patients, a gastrinoma located in the duodenum and the presence of localized disease were associated with a positive secretin test result (Table 8). In the literature ZES patients only, male gender and lack of previous acid-reducing surgery associated with increased likelihood of a positive result (Table 8).

With the calcium test using the Δ calcium≥395 pg/ml criterion [78], the most commonly used criterion [166,397], no clinical, laboratory or tumor variable affected the positivity in ZES patients. No clinical, laboratory or tumoral variable, except MEN1 status or previous gastric

acid-reducing surgery, influenced the occurrence of <50% increase in serum gastrin post meal, a response characteristic of ZES patients [31,195,196,347] (data not shown).

Comparison of four doses of secretin for provocative testing (Table 9)

In the past, different doses of secretin have been used for provocative testing (Table 9). While 2 units of secretin per kg body weight is the most commonly used dose today, in some studies, doses of 1 unit/kg, 75 units, 3 units/kg or even higher doses have been used (Table 9). We compared the percentage of positive tests using different doses of secretin in literature patients (Table 9). Similar to some studies [189,219,380], but not others [153,229,329,405] there was no apparent secretin dose-response effect using any criterion either for all patients or for patients with FSG<10-fold increased. Specifically, results with 1 unit/kg or 3 units/kg secretin were similar and no increased detection occurred with the higher dose (Table 9). Moreover, secretin tests with 75 units and 2 units/kg also gave similar results (Table 9).

FSG and secretin provocative test results in non-ZES patients (Table 10)

To assess the specificity of secretin and calcium provocative tests, we analyzed results from the literature in non-ZES patients (Table 10). Because high FSG levels and false positive gastrin provocative tests can occur in patients with achlorhydria [42,98,141,192,219], we analyzed results separately for this patient group. Of the 462 subjects without ZES and without achlorhydria who underwent secretin testing (normal controls, patients with antral G-cell hyperplasia, moderate hypochlorhydria or peptic ulcer disease), FSG levels were reported in 147 patients and the majority had either a normal or only moderately elevated FSG value (Table 10). None of the 462 non-ZES patients had a positive secretin test using the Δ≥200 or Δ≥110pg/ml criterion and 1 out of 462 (0.22%) had Δ>100 pg/ml (Table 10). Sixteen patients (7%) had a positive secretin test using the >50% criterion, 3 (1%) using the criterion Δ>100%, 17 patients (13%) using the criterion of Δ ≥186 pg/ml and 5 patients (4%) using the criterion of ≥ 335 pg/ml increase (Table 10). Hence, overall, the Δ criteria had better specificity than the % increase or maximal gastrin value criteria (Table 10). In patients with achlorhydria, false positive secretin tests were more common (Table 10), emphasizing the importance of excluding these patients. One hundred non-ZES subjects without achlorhydria who underwent calcium provocative tests could be found in the literature (Table 10). Overall, false positive calcium tests occurred more frequently with the percentage criteria.

Sensitivity and specificity of different criteria for positive provocative tests using secretin (Table 11)

Data from ZES and non-ZES patients were used to estimate sensitivity and specificity of secretin tests in the clinically relevant group of patients with <10-fold FSG increase (Table 11). As the Δ criteria offered better specificity (Table 10), only these criteria were considered for analysis. Both the proposed Δ criteria of >100 [77], Δ≥110 [78] and ≥ 200 pg/ml [238] increase were analyzed as well as new possible criteria of an increase of ≥120, ≥130, ≥140, ≥150, ≥160, ≥170, ≥180 or ≥190 pg/ml (Table 11). As the highest increase in serum gastrin occurring in a normal subject was 101 pg/ml, delta criteria of ≥110 to ≥200 pg/ml had 100% specificity. The sensitivity of the proposed criterion of Δ≥ 200 pg/ml was 87%, which is significantly less ($p<0.05$) than the 91% sensitivity of a Δ≥140 criterion, highly significantly

different ($p<0.01$) from $\Delta \geq 130$ pg/ml and even more significantly different ($p<0.003$) from a criterion of $\Delta \geq 120$ pg/ml. From this analysis, the criterion with 100% specificity and highest sensitivity is Δ secretin ≥ 120 pg/ml.

Discussion

In this study, we prospectively analyzed the increase in serum gastrin after provocative tests in 293 ZES patients and compared our results to data from 537 patients from the literature. In the accompanying paper [30], we found that the determination of FSG levels alone cannot establish the diagnosis in two-thirds of ZES patients, because FSG levels of ZES patients significantly overlap with those seen in idiopathic peptic disease or other non-ZES conditions [78,151,152,217]. Therefore, several gastrin provocative tests have been developed. These tests use different stimuli including calcium infusion or bolus injection [196,295,318,380], infusion or bolus injection of secretin [31,153,192,196,247,252], administration of a meal [31,196,348] and injection of glucagon [26,69,153,183,183,265,343,360] or bombesin [22–24,158]. Only the secretin (bolus), calcium (infusion) and meal tests are generally used today [78,110,111,167,196,219,238,250,397]. Due to methodological inconsistencies in previous studies, the criteria for each of these tests remain an area of controversy and some studies even question their overall usefulness.

Since the initial description of the ability of secretin to stimulate an exaggerated serum gastrin increase in ZES patients [137,153], the secretin test has been increasingly used in the diagnosis of ZES [110,238,394,397]. Although some studies have proposed that this increased response represents an exaggerated normal response [40,44,45], there is strong evidence that secretin can stimulate gastrin release by direct interaction with gastrinoma cells. Secretin receptors occur on gastrinoma cells [84], secretin stimulates gastrin release from isolated gastrinoma cells [58,93,129,129,147] and this effect can be inhibited by somatostatin [58].

In the literature, some ZES patients have no increase in FSG after a bolus injection of secretin [73,94,219,229,230,233,247,318,341,343,344,351,360,405,406]. The percentage of these patients varies from 0% in most studies [78,150,157,189,196,240,255,315] to 7–75% [229,247,318,343,344,360]. In larger series however, most patients had a significant increase in FSG post secretin (median 262–1103 pg/ml in 10 large studies [66,78,100,150,196,218,232,315,341,412]). In our study, only 1.4% of literature or NIH ZES patients had no increase in serum gastrin after secretin, demonstrating that >98% respond to secretin. Our results demonstrate that in ZES patients, no response to secretin injection is very uncommon.

Numerous studies have proposed criteria for a positive secretin test [77,78,110,196,219,260,301]. However, these criteria vary widely, which is primarily due to multiple methodological differences. Some studies are limited by small patient numbers (<25 patients) and patients with FSG< or >10-fold increased are usually considered together, although provocative tests are of clinical relevance only in the former group [78,110,152,196,342,344,360]. Moreover, different protocols and different secretin preparations have been used (Boots, GIH, synthetic), which is relevant because false positive secretin tests have been reported with Boots secretin [41,238,398]. Different modes for secretin administration have been employed (infusion, bolus injection) [238,247,249,250,252,301] and different doses used. The secretin dose

could be relevant because some studies [153,229,238,405], but not others [153,229,329,405], report that different doses may give different results. Our systematic analysis of secretin test results in patients receiving different doses of secretin (1 U/kg, 75 U total, 2 U/kg, ≥3 U/kg) showed no dose-response effect (Table 9). These results are similar to some studies [189,219,380], but not others [153,229,329,405], and led us to conclude that there is no need to increase the usual 2 units/kg dose or to repeat a secretin study with a higher dose if the initial study was negative, as suggested by others [229,405]. Furthermore, secretin test protocols frequently varied in the time points for collection of blood samples. This is important because some studies did not measure gastrin 2 minutes after secretin injection [196,255]. In one study [110] however, 6% of ZES patients had their only positive response 2 minutes post injection. Moreover, these studies were further limited by small patient numbers (<25 patients) and the fact that patients with FSG< or >10-fold increased were considered together, although gastrin provocative tests are of clinical relevance only in the former group [78,110,152,196,342,344,360].

Three different types of criteria for a positive secretin test have been proposed: 3 criteria based on the absolute increase in FSG post secretin (>100, ≥110, ≥200 pg/ml) [77,78,110], 2 criteria based on the relative increase (i.e. >50%, >100%) [196,260] and 2 criteria based on the maximal FSG level post secretin (i.e. ≥186 or ≥335 pg/ml) [219,301]. Based on a review of 122 cases from the literature [238], the criterion of ≥200 pg/ml increase post secretin has been most widely used since 1980 in the United States [110,119,166,397]. Because we had a large number of patients, we could systematically assess the sensitivity of the various proposed criteria, both in all patients and the clinically important subset of ZES patients with FSG<10-fold increased [78,110,152,196,342,344,360]. In NIH and literature ZES patients, 3 criteria had sensitivities of 90–100% (Δ>100 pg/ml, Δ≥110pg/ml, gastrin max. ≥186 pg/ml) and 3 had sensitivities of 85–89% (Δ≥200 pg/ml, Δ>50%, gastrin max.≥335 pg/ml). One proposed criterion, Δ>100%, had a low sensitivity of only 60–62%, suggesting it is not generally useful. Because ZES is an uncommon condition (1–3 cases/year/million population) and hypergastrinemia due to H. pylori infection or other conditions is much more frequent [78,90,151,152,203,217,236,246,337], it is very important to limit false positive responses, so that the specificity may be the most important factor in determining an optimal secretin test criterion. To assess the specificity of the six different secretin test criteria with high sensitivity (85–100%), we analyzed the results from 489 non-ZES patients' responses from the literature (Table 10), including 462 without and 27 subjects with achlorhydria. Because there was an unacceptably high false positive rate varying from 7% to 100% in achlorhydric patients, our analysis confirms the proposal that secretin test results are not reliable in these subjects [42,98,141,192,219]. After exclusion of achlorhydric patients, the 3 absolute increase criteria (i.e.Δ >100, ≥110, ≥ 200 pg/ml) gave very low false positive rates (0–0.5%) resulting in a specificity of 99.8–100%, whereas the remaining highly sensitive criteria (Δ>50%, gastrin max. ≥186 pg/ml, gastrin max. ≥ 335 pg/ml) gave higher false positive rates of 4–13%. Our analysis demonstrated that the proposed criteria with the highest sensitivity and specificity are Δ≥100 pg/ml [95%, 99.8%], Δ≥110 pg/ml [94%, 100%] and Δ≥200 pg/ml [87%, 100%]. Because the sensitivity of the Δ>100 and Δ≥110 criteria was significantly higher than that of Δ≥200 pg/ml, we tried to identify a new criterion with maximal sensitivity and 100% specificity. This criterion is a Δ≥120 pg/ml, which has 94% sensitivity and a specificity of 100%. Both the Δ≥120 and Δ≥130 pg/ml criteria had a 100% specificity and each had

a significantly higher sensitivity than the commonly used Δ≥200 pg/ml criterion (Table 11). The Δ≥120 pg/ml criterion had the same sensitivity as the previously proposed Δ≥110 criterion [78] (i.e. 94%) and its sensitivity was not significantly different from that of the Δ>100 criterion [77]. However, in the non-ZES patients without achlorhydria, one patient had an increase in serum gastrin after secretin of 101 pg/ml and 4 patients had an increase of 100 pg/ml. Therefore, we conclude that Δ≥120 pg/ml was the criterion with maximal sensitivity and 100% specificity. Criteria of ≥110 and ≥120 pg/ml both had equal sensitivity and 100% specificity, but because of the importance of limiting a false positive result to the greatest extent, we recommend a criterion of Δ≥120 pg/ml rather than 110 pg/ml as recommended by others [78].

Based on these results, we suggest that a secretin test should be performed with 2 units GIH or synthetic secretin per kg body weight, it should include an assessment of serum gastrin before secretin injection, and 2, 5, 10, 15 and 20 minutes [110] after secretin. An absolute increase in serum gastrin ≥ 120 pg/ml should be the criterion for positivity because it has the highest sensitivity with 100% specificity (Table 11). When this new criterion is applied to the 453 NIH and literature ZES patients in our study with FSG<10-fold increased, it allows the correct diagnosis of 37 ZES patients that would have had a negative test with the commonly used the 200 pg/ml criterion.

Numerous studies show serum calcium levels can greatly influence FSG in ZES patients with or without MEN1. Intravenous administration of calcium augments basal hypergastrinemia [69,78,157,181,197,212,237,295,311,361,368,368,386], whereas a reduction of calcium levels by EDTA administration [157,388] or correction of hyperparathyroidism by parathyroidectomy [59,87,88,127,153,159,276,361,368,369,393] diminishes hypergastrinemia in ZES patients. This calcium-induced augmentation of FSG in ZES patients is the basis of the calcium provocative test [69,197,262,295,360,368]. Subsequent studies have shown that this effect is likely due to a direct action of calcium on gastrinoma cells [2,33,91,93,399,400]. In fact, calcium can increase gastrin release from isolated gastrinoma cells [2,33,91,93,399,400]. Furthermore, these cells possess both calcium sensing receptors and various calcium channels [126,155,378] whose activation could stimulate gastrin secretion.

In previous reports [69,78,192,196,197,219,255,295,343,360], very few ZES patients did not respond to an intravenous calcium infusion [195,233,351] and the median FSG increase was 438–4325 pg/ml in 8 larger series [23,78,110,196,232,262,318,341]. In our study, 6 NIH and 3 literature ZES patients did not respond to calcium, demonstrating that calcium evokes an increase in serum gastrin in >97% of ZES patients. The median increase was 850 pg/ml in NIH and 994 pg/ml in literature patients.

Numerous authors have proposed different criteria for a positive calcium test [77,78,196,219,260]. With the exception of two studies advocating a bolus injection of calcium [318,380], these studies used very similar protocols (dose of calcium, time of infusion, time points for blood collection). Nevertheless, their results are limited by small patient numbers and the fact that patients with a FSG<10 and >10-fold increased are considered together. Three different types of criteria have been proposed for a positive calcium test: 2 criteria based on the absolute increase in FSG post calcium (≥450, ≥395 pg/ml) [77,78], 2 criteria based on the

relative increase (>50%, >100%) [196,260] and 1 criterion based on the maximum FSG level post calcium (≥326 pg/ml) [219]. In the United States, the criteria of ≥395 pg/ml and >50% are widely used [78,110,196]. We found that 1 criterion had >90% sensitivity (gastrin max. ≥326 pg/ml), 1 criterion had 79–90% sensitivity (Δ>50% increase) and 3 criteria had 57–76% sensitivity (Δ≥450, ≥395 pg/ml, >100%). In patients with <10-fold increase in FSG the sensitivities of the two criteria based on absolute increases dropped 5–13%, whereas there was no relevant decrease in sensitivity for the other criteria. For the two criteria generally used in the United States (Δ≥395 pg/ml or >50% increase), the sensitivities in the NIH/literature patients were 54/70% and 78/91%, respectively. As discussed above, avoiding false positive tests is especially important. An analysis of the available data from 105 non-ZES patients who underwent calcium testing allowed us to assess the specificity of the different criteria. As the calcium test may be falsely positive in up to 50 % of non-ZES patients with achlorhydria [196,219], only non-ZES patients without achlorhydria were included in this analysis. The Δ>50% and Δ>100% criteria gave an unacceptably high number of 10–17% false positives, whereas only one non-ZES patient exceeded the gastrin max. ≥326 pg/ml criterion. However, this last criterion is not clinically useful because most patients with a FSG<10-fold increased (64% in our study) have a fasting serum gastrin ≥326 pg/ml prior to any stimulation. No non-ZES patient without achlorhydria in the literature had an increase in serum gastrin post calcium ≥ 395 pg/ml, so that the Δ≥450 and Δ≥395 pg/ml criteria have 100% specificity. The ≥395 pg/ml criterion had a greater sensitivity than the ≥450 pg/ml criterion, although this difference did not quite reach statistical significance ($p>0.1$). Nevertheless, it could be clinically relevant because the calcium test is generally used as second-line test in patients with strong clinical suspicion of ZES but a negative secretin test. Therefore, maximal sensitivity, along with 100% specificity, is crucial for choosing the optimal criterion. Taking this into account, we conclude that Δ≥395 pg/ml should be used. However, even with this criterion, the sensitivity of the calcium test is significantly lower than that of the secretin test (63 vs. 94%, $p<0.01$). Furthermore, unlike with secretin, numerous side-effects are reported with the infusion of calcium, including abdominal pain, nausea, vomiting, headache, phlebitis, shortening of Q-T interval on ECG, paresthesias, diuresis, severe fatigue, palpitations, arrhythmias and a rise in blood pressure [110,177,196,255,318,380]. These complications lead to early termination of the infusion in some patients [318]. Moreover, the calcium infusion test takes longer than the secretin test (3 hr. vs. 30 min) and requires a physician's attendance. In addition, the secretin test may be superior to calcium testing in distinguishing antral from tumoral hypergastrinemia [182,190,196,347]. For these reasons, we conclude the calcium test should not be used routinely as the first-line test in patients suspected of having ZES. However, in one previous study [110], 33% of ZES patients with a negative secretin test had a positive calcium test. Two smaller series report secretin-negative ZES patients with a positive response to calcium infusion [318] or injection [380], whereas another study reports negative calcium tests in all secretin-negative ZES patients [196]. In our study, 38% of NIH and 50% of literature ZES patients with a negative secretin test (applying the Δ≥120 pg/ml criterion) had a positive calcium test (by the Δ≥395 pg/ml criterion). Therefore, we conclude that the calcium test is useful in patients with a clinical suspicion of ZES but a negative secretin test.

Ingestion of food is a physiological stimulus for the release of gastrin from the antral and duodenal mucosa [31]. In patients with hypergastrinemia of antral origin, i.e. atrophic gastritis or antral G-cell hyperfunction, a condition reported to occur in H. pylori infection [9], feeding induces an increase >100% in FSG[31,83,114,158,176,204,300]. In ZES patients, gastrin produced by the tumor is the main source of serum gastrin and early studies reported no major increase in FSG after ingestion of a test meal, suggesting that feeding does not stimulate gastrin release from gastrinomas [31,152,158,190,195,264,347]. Therefore, it was proposed that a standard meal test could differentiate hypergastrinemia of antral and tumoral origin [31,347]. This is an important distinction because antral G-cell hyperplasia/hyperfunction can mimic ZES clinically and cause hyperchlorhydria/hypergastrinemia [6,7,167,186,194,204,299,397]. However, other studies have reported ZES patients with large increases in FSG after feeding and questioned the value of the meal test [69,111,196,343]. The mechanism of postprandial FSG increase in ZES patients is controversial. Some studies suggest the gastrin could be of antral origin in patients having both ZES and antral syndromes [106], while other authors propose the gastrin release is mediated by the tumor [111], possibly involving release of a gastrin-stimulating agent, e.g. secretin, from the duodenum [359,360]. Some reports suggest that previous gastric surgery could influence the increase in gastrin post meal in ZES patients [69,111,195,360]. The small number of ZES patients investigated, the different proportion of patients with prior gastric surgery and differences in tumor characteristics could partly explain the large discrepancies between some of these studies (Table 12). In our study, 39% of NIH and 20% of literature patients had no increase in serum gastrin post meal. In the remaining patients, the median increase was 132 pg/ml among NIH and 212 pg/ml among literature ZES patients. In five larger series, the median increase in FSG post meal was 55–2269 pg/ml [69,158,196,198,360]. In our present study, meal test results did not differ in ZES patients with or without prior acid-reducing surgery (median increase 175 vs. 223 pg/ml, p=0.2).

Lamers and van Tongeren proposed a postprandial increase <50% to be characteristic of ZES [196]. In another study, a maximal serum gastrin value post meal >500 pg/ml was suggested as criterion. However, this latter criterion is of little clinical value because it does not differentiate antral hypergastrinemia from ZES and is not applicable to ZES patients with a FSG >500 pg/ml. In our study, 57% of NIH and 67% of literature ZES patients had an increase in serum gastrin post meal <50%. These numbers change to 54 and 77%, among patients with FSG<10-fold increased. However, 20% of NIH and 15% of literature ZES patients had an increase in FSG post meal ≥100%, a value reported to be characteristic of antral G-cell hyperplasia [7,9,108,111,158,167,204,336,347]. Because of this overlap of meal test results in patients with hypergastrinemia of antral or tumoral origin, we conclude, in accordance with others [69,111,219], that the meal test is not useful in the diagnosis of ZES.

Only very limited information is available on correlations of gastrin provocative test results with clinical, laboratory or tumoral features in ZES. However, these correlations might be useful because they could define a subgroup of clinically relevant patients. Moreover, such correlations could identify patients in whom provocative test results are not conclusive because they are biased by different factors. In accordance with previous studies [196,318], we found a positive correlation (r=0.52–0.56) between the absolute increase in FSG after secretin and calcium (Figure 5). This correlation remained unchanged if the relative (%)

increases were correlated, suggesting that the correlation is not due to the influence of FSG levels on both variables, but rather reflects common factors may be involved in determining the response to both stimulants. Our study did not identify these factors, but they could include the response of the gastrinoma to external stimuli, the amount of gastrin stored or shared pathways of stimulation. Similar to other studies [42,315], we found that secretin and calcium test results were both correlated with FSG values when the absolute increases post stimulation (Δ) were considered (Figure 2). However, this correlation was not significant after correction for higher FSG values by correlating the relative increases. We found a correlation of secretin and calcium test results with BAO levels and with some clinical findings (duration of medical treatment, diarrhea) associated with gastric hyperacidity [319] (Tables 4–6 and Figure 3). Most interestingly, MEN1 patients, who frequently have hypercalcemia due to hyperparathyroidism [29,123,221], did not show a significantly greater serum gastrin response to secretin (Table 5). This finding is surprising because hypercalcemia facilitates secretin-induced gastrin release in ZES patients [157,196,318]. In our study, we found that larger tumors are associated with a higher response to secretin or calcium (Tables 4–6, Figures 3, 4). The size of the largest tumor correlates better with FSG increases post secretin than primary tumor size. This correlation is even stronger in patients without liver metastases, suggesting that the absolute tumor mass rather than the characteristics of the primary tumor influences the response to secretin. While these clinical, laboratory or tumor variables had some influence on the magnitude of the serum gastrin response to secretin, they had little effect on the positivity of the provocative test results. This finding has clinical importance because it shows that clinical, laboratory or tumor features do not bias provocative test results with secretin or calcium and that these tests can therefore be performed in subgroups of ZES patients with different characteristics.

As discussed above, our data suggest that the meal test is generally not helpful in the diagnosis of ZES. However, correlations of the increase in serum gastrin post meal in ZES patients with clinical, laboratory and tumor features might allow some insight into ongoing controversies concerning meal-stimulated gastrin release. Some authors propose that the postprandial gastrin release in ZES patients could be mediated by the release of a gastrin-stimulating agent, such as secretin, from the duodenum [359,360]. If secretin were involved in postprandial gastrin release, patients with increases in serum gastrin post meal might have a proportional response to secretin. Therefore a significant correlation might exist between secretin and meal test results. However, we did not find such a correlation (Figure 5). Because Billroth II resection results in markedly diminished meal-stimulated secretin release [268,269], our finding of similar meal test results in ZES patients with or without previous Billroth II resection further invalidates the hypothesis of a secretin-mediated mechanism for postprandial gastrin release in ZES patients. It has been suggested that the increase in serum gastrin post meal observed in some ZES patients could be due to coexisting antral G-cell hyperplasia/hyperfunction [106]. Because the meal response is markedly affected by gastrinoma resection in ZES patients[111], this proposal is unlikely. MEN1/ZES patients are reported to have an increased incidence of antral syndromes in some studies [106], but not in others [111]. Our data do not support this proposal, because we found that prior antrectomy does not influence meal test results in ZES patients. However, our data did show that NIH MEN1/ZES patients had a significantly higher median FSG increase post meal than

sporadic ZES patients (Table 7) and a significantly higher percentage of these patients had a ≥50% postprandial FSG increase. This difference could be related to other factors than an increased occurrence of antral syndromes, such as concomitant hyperparathyroidism with hypercalcemia, which could affect meal-stimulated hormone release. It has been suggested that duodenal gastrinomas are associated with higher postprandial FSG increases than pancreatic tumors [196], whereas another large study did not find such a correlation [111]. In our study, we found that patients with duodenal gastrinomas have larger postprandial serum gastrin increases (Table 7). However, this did not affect meal test results, i.e. the percentage of patients with ≥ 50% increase in serum gastrin post meal. Therefore our result is similar to another study [111] and suggests that the meal test is not useful in localizing duodenal gastrinomas.

Our results for secretin testing in general show similarities to most other series including ≥10 patients, however, they also show some important differences (Table 12). Specifically, we found the most widely used criterion of ≥200 pg/ml does not have a sensitivity of 100% as reported in a number of studies [66,238,341,412] or a low sensitivity of 70–80% as reported in other studies[78,232]. Our results agree with a number of other series reporting a sensitivity of 83–86% [100,315] (Table 12). Similar to most studies, we found the criterion of Δ≥110 pg/ml to have a higher sensitivity (92–100%) and the >50% criterion to be less sensitive than either the Δ≥110 or Δ≥200 pg/ml criteria (Table 12). For the calcium test, a number of studies reported a higher sensitivity than we found, especially for the 50% criterion [23,78,232,318,341], while others had results comparable to those of our study [262] (Table 12). This difference in sensitivity cannot be due to a difference in the amount of calcium infused because in most studies, 5 mg/kg/hr of calcium was infused for 3 hours and all patients had at least a 1.5 mEq/l increase in serum calcium. The meal test results in our study are comparable to results reported in some series, [69,347,360], but markedly differ from results of other studies which reported no ZES patients with a ≥100% increase in serum gastrin post meal [157,196,216] (Table 12).

The systematic analysis of gastrin provocative test results in 293 NIH and 537 literature ZES patients presented in this paper allowed us to draw several important conclusions which are summarized in Table 13. We could show a new criterion, Δ≥120%, which had the highest sensitivity and specificity. When this new criterion is applied, the secretin test is highly sensitive (94%) and specific (100%) and therefore play a crucial role in the diagnosis of ZES in the two-thirds of patients with non-diagnostic FSG values. This new criterion had greater sensitivity ($p<0.003$) than the usually used criterion of Δ≥200 pg/ml with equal specificity (i.e. 100%) and allowed the detection of 37 more ZES patients in the NIH and literature groups than the Δ≥200 pg/ml criterion. We applied the same analysis to calcium test results and could confirm the usefulness of the Δ≥395 pg/ml criterion proposed by others [78]. However, even with this criterion, the calcium test has only a 62% sensitivity. Furthermore, multiple side-effects have been reported with intravenous calcium infusion. Therefore, the calcium test should not be used as first-line provocative test. However, the calcium test may be useful in patients with a negative secretin test, but strong clinical suspicion of ZES because it will be positive in 38–50% of these ZES patients. We could not confirm the utility of the meal test, because we found significant overlap of meal test results in patients with ZES and antral syndromes. We found the magnitude of the gastrin response to secretin and

calcium to correlate with BAO values and some clinical findings reflecting hyperchlorhydria as well as with tumor size and extent. However, the results (i.e. positive or negative) of these tests were only minimally influenced by these factors. The magnitude of the meal-induced gastrin response correlated with some clinical findings, including MEN1 status, and with tumor location. However, meal test results were only minimally influenced by these factors, so that the meal test is not useful for tumor localization.

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Abbreviations used in this article:

Δ calcium	Increase in serum gastrin post calcium
Δ meal	Increase in serum gastrin post meal
Δ secretin	Increase in serum gastrin post secretin
BAO	Basic acid output
FSG	Fasting serum gastrin
GIH secretin	Gastro-intestinal hormones secretin, Karolinska Institute, Stockholm, Sweden
MAO	Maximal acid output
MEN1	Multiple Endocrine Neoplasia type 1
MRI	Magnetic resonance imaging
NIH	National Institutes of Health
PPI	Proton pump inhibitor
PTH	Parathormone
RIA	Radioimmunoassay
ZES	Zollinger-Ellison syndrome

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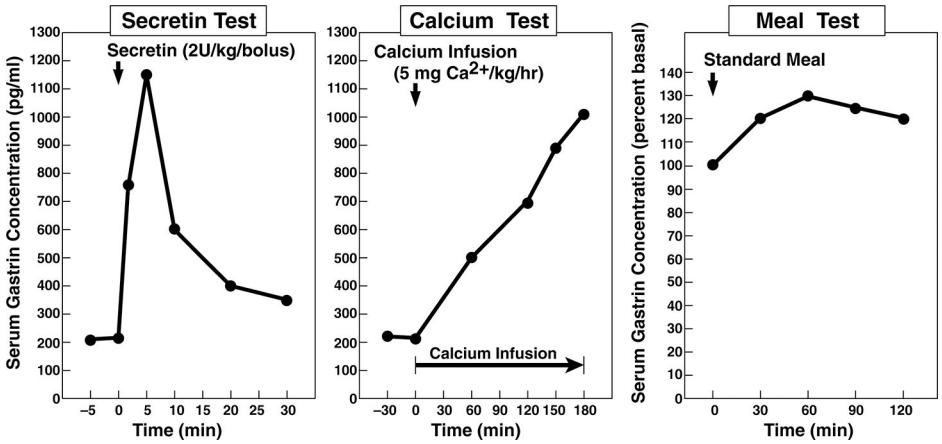

Figure 1.

Secretin, calcium and meal gastrin provocative test results from the ZES patient in the case presentation. Left Panel. Secretin (2 units/kg IV bolus) was given at zero time and serum gastrin was measured at −5,0,2,5,10,15,20 and 30 min post secretin injection. This ZES patient shows the rapid increase in serum gastrin post secretin characteristic of patients with ZES [78,110,153,196,238,250]. Middle panel. A calcium infusion of 5 mg/kg/hr was started at 0 time and give for 3 hours as indicated by the solid bar. Serum gastrin levels were measured at −30,0,60,120,150 and 180 min after the infusion was begun. This ZES patient shows the characteristic slow rise in serum gastrin characteristic of patients with ZES [78,110,196,255,295]. Right panel. A standard meal was given at 0 time and serum gastrin measured at −15, 0 30,60,90 and 120 min post meal. This ZES patient shows less than a 50% increase in serum gastrin post meal which is reported to be characteristic of patients with ZES and in contrast to patients with antral G cell hyperplasia/hyperfunction which have an exaggerated response (i.e.>100% increase) [7,9,167,196,204]

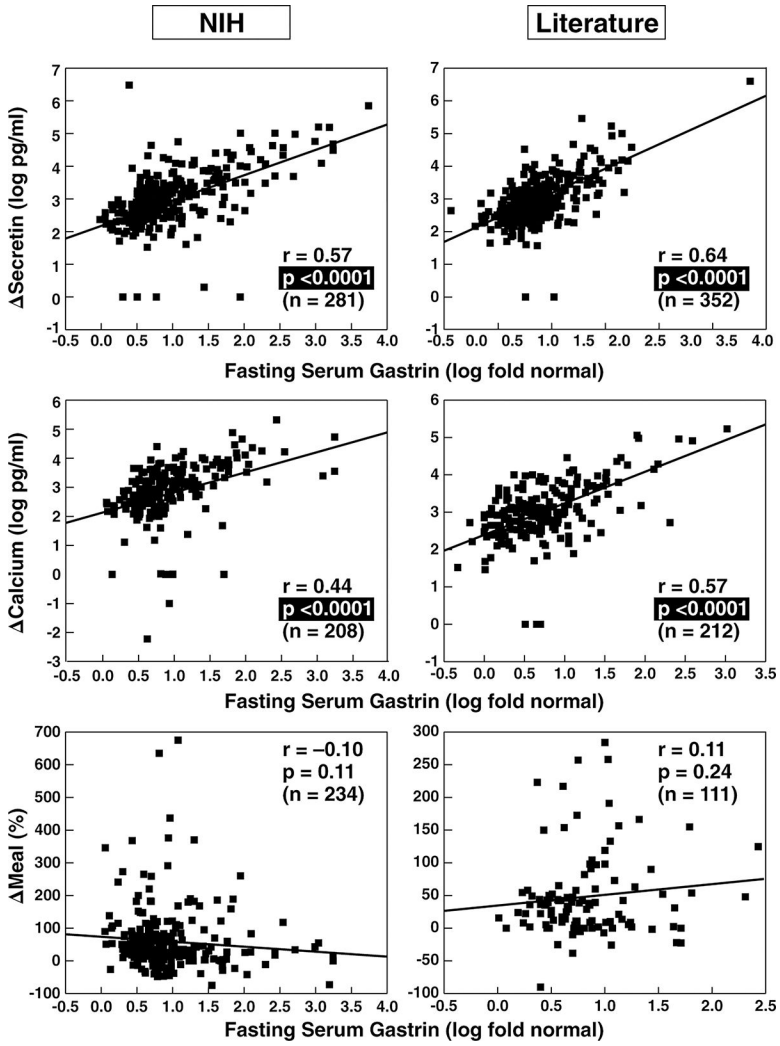

Figure 2.

Correlation between fasting serum gastrin and secretin, calcium and meal provocative test results in ZES patients. Data from 280 NIH patients and 355 from the literature are shown. The correlation between the fasting serum gastrin level expressed as a fold increase and the absolute change in serum gastrin concentration after secretin injection (upper panels) or calcium infusion (middle panels) as well as the relative change in serum gastrin concentration after a standard meal (lower panels). Each point represents data from one patient. Indicated are the regression line and the correlation coefficient (r) using a least-squares analysis. Literature data are from publications listed in Table 2.

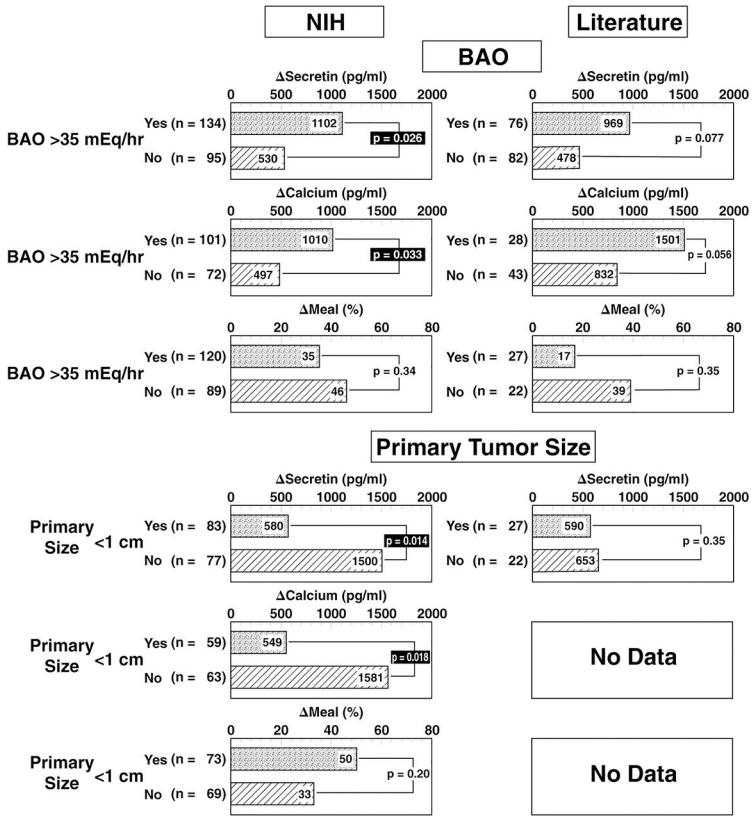

Figure 3.

Effect of the magnitude of basal hyperchlorhydria or primary tumor size on provocative test results after stimulation with secretin, calcium or a standard meal. Indicated is the median value of the absolute (secretin, calcium) serum gastrin increase after stimulation in ZES patients from NIH and from the literature. The meal results are expressed as the median percentage gastrin increase over the pretreatment value. Literature data are from publications listed in Table 2. Insufficient data on primary tumor size in patients in the literature was found to allow comparison of this variable in literature patients. Only patients without previous gastric acid-reducing surgery were included in the analysis of the effect of BAO and only patients without liver metastases were included in the analysis of the effect of primary tumor size. Numbers in parenthesis refer to number of patients with the indicated variable.

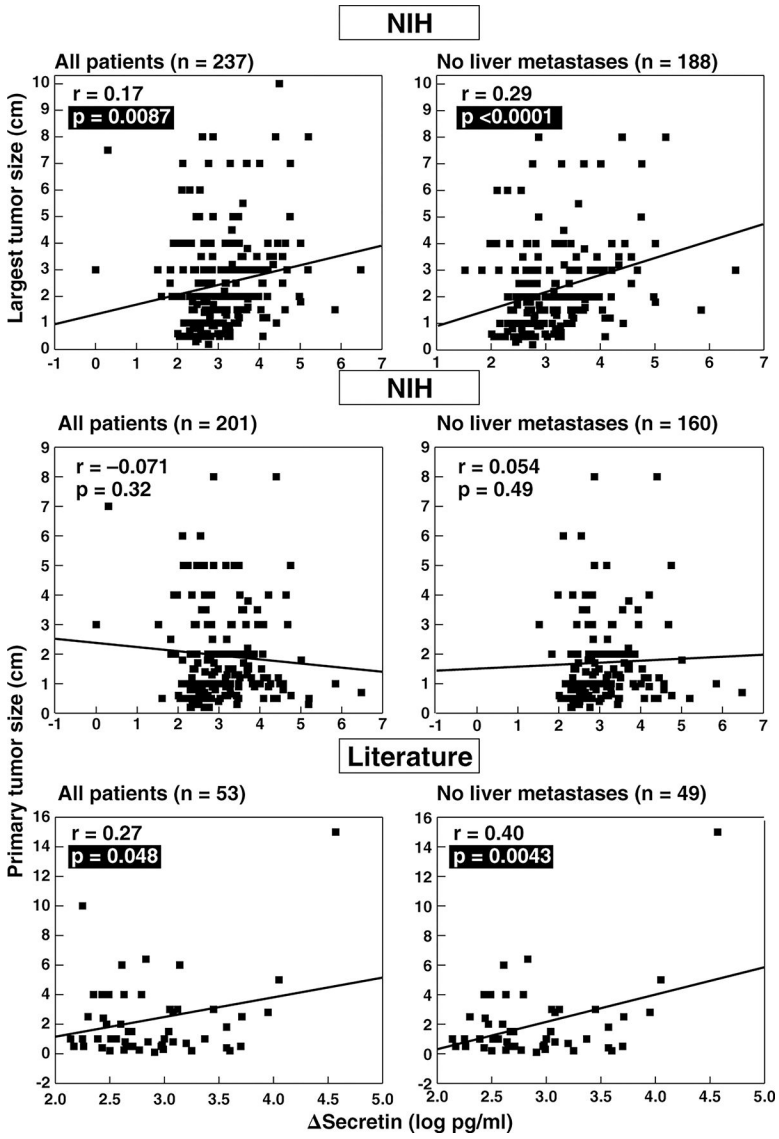

Figure 4.

Correlation between tumor size and secretin test results in ZES patients. The top panels show the correlation between the size of the largest tumor found at surgery or by imaging and the absolute change in serum gastrin after secretin injection (Δ secretin) in ZES patients from the NIH with and without liver metastases. The Δ secretin is expressed as the log of the change is serum gastrin with secretin. The middle and bottom panels show correlations of primary tumor size in ZES patients from NIH and from the literature with the Δ secretin. Each point represents data from one patient. Indicated are the regression line and the correlation coefficient (r) using a least-squares analysis. Literature data are from publications listed in Table 2. Tumor size is expressed as cm in diameter.

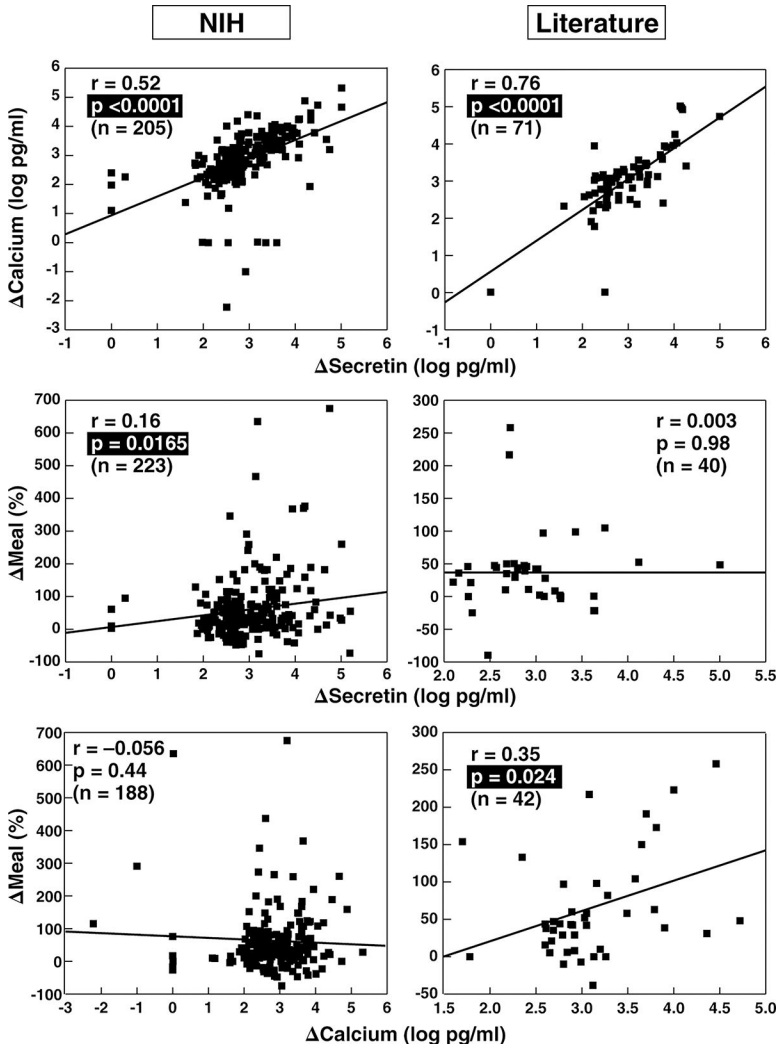

Figure 5.

Correlation between secretin, calcium and meal provocative test results in ZES patients from the NIH (n=223) and the literature (n=71). Represented is the correlation between the absolute changes in serum gastrin concentration after secretin injection (Δ secretin) or calcium infusion (Δ calcium) (upper panels); the correlation between Δ secretin and the relative change in serum gastrin concentration after a standard test meal (Δ meal)(middle panels) and the correlation between Δ calcium and Δ meal (bottom panels). Each point represents data from one patient. Indicated are the regression line and the correlation coefficient (r) using a least-squares analysis. Literature data are from publications listed in Table 2.

Table 1.

Comparison of clinical characteristics, laboratory data and tumor features in 293 ZES patients seen at NIH and 537 ZES patients from the literature who underwent gastrin provocative testing.

Characteristic	No. (%)* NIH	Literature	p
Number of patients	293	537	
Male gender	160/293 (55)	264/436 (61)	0.11
Age at evaluation (yr)			
Mean ± SEM [Range]	47.9 ± 0.6 [15–71]	46.3 ± 0.65 [15–80]	0.15
MEN1 present	85/293 (29)	105/489 (21)	0.017†
Previous acid-reducing surgery‡	44 (15)	93 (17)	0.39
Acid secretion (no previous acid-reducing surgery)§			
BAO (mEq/hr)			
Mean ± SEM [Range]	43.4 ± 1.6 [1.8–159]	28.8 ± 1.7 [1.9–143]	0.0077†
MAO (mEq/hr)			
Mean ± SEM [Range]	63.5 ± 2.1 [3.8–159]	52.1 ± 2.3 [4–149]	<0.0001†
Acid secretion (previous acid-reducing surgery)**			
BAO (mEq/hr)			
Mean ± SEM [Range]	27.1 ± 3.1 [2–94]	16.5 ± 1.7 [1–66]	0.0009†
MAO (mEq/hr)			
Mean ± SEM [Range]	38.3 ± 4.8 [2–140]	29.4 ± 3.2 [3–90]	0.14
Gastrin††			
Fold fasting serum gastrin‡‡			
Median [Range]	6.37 [0.96–5500]	4.83 [0.13–50000]	<0.0001†
Δ secretin (pg/ml)			
Median [Range]	744 [0–3000000]	600 [−536–4000000]	0.048†
Δ calcium (pg/ml)			
Median [Range]	850 [–10–208000]	994 [0–168000]	0.29
Δ meal (pg/ml)			
Median [Range]	212 [−40000–60000]	132 [−1750–35102]	0.082
Primary tumor localization			
Pancreatic	81/293 (28)	107/300 (36)	0.036†
Duodenum	110/293 (38)	68/300 (23)	<0.0001†
Other§§	36/293 (12)	35/300 (12)	0.81
Unknown***	78/293 (27)	96/300 (32)	0.15
Tumor extent			
Localized disease)†††	247/293 (84)	160/227 (70)	0.0004†

		No. (%)*	
Characteristic	**NIH**	**Literature**	**p**
Distant metastases ###	46/293 (16)	67/227 (30)	0.0004†

Abbreviations: ZES: Zollinger-Ellison syndrome, NIH: National Institutes of Health, yr: years, SEM: standard error of the mean, MEN1: multiple endocrine neoplasia type 1, BAO: basal acid output, MAO: maximal acid output.

*Numbers in denominator are numbers of patients with data available.

†indicates a significant difference ($p<0.05$).

‡Including patients with partial gastrectomy (literature 66, NIH 23), vagotomy/drainage (literature 45, NIH 17) and total gastrectomy (literature 15, NIH 6).

§BAO data from 230 literature and 240 NIH patients, MAO data from 152 literature and 202 NIH patients without previous acid-reducing surgery.

**BAO data from 73 literature and 39 NIH patients, MAO data from 45 literature and 36 NIH patients with previous acid-reducing surgery..

††Data on fasting serum gastrin available for all patients, secretin tests for 355 literature and 279 NIH patients, calcium stimulation for 212 literature and 207 NIH patients, the meal test data for 112 literature and 229 NIH patients. The Δ calculated for the stimulation tests corresponds to the difference between the gastrin value showing the greatest change after stimulation and the basal gastrin value.

##Expressed in fold of the highest normal value.

§§'Other' includes 16 primary tumors of the lymph node, 4 gastric, 6 ovary, 5 liver, 2 jejunal for the literature data; 20 lymph node, 5 liver, 3 stomach 2 bile duct, 2 heart, 1 jejunum, 1 omentum and 1 lung tumor for the NIH patients.

***'Unknown' includes patients without tumor evidence on imaging studies who did not undergo surgical exploration or for whom surgical data was not available.

†††Only patients with no evidence of liver or other distant metastases

###Including 60 patients with liver metastases, 1 lung, 3 bone, 1 peritoneal and 1 duodenal for the literature patients and 45 liver metastases for the NIH patients.

Table 2.

Results of provocative tests with secretin, calcium or a standard meal in ZES patients seen at NIH and Zollinger-Ellison patients from the literature.

	No. (%)		
	NIH	**Literature**	**p**
Δ post secretin (pg/ml) *	**(n=280)**	**(n=355)**	
Decrease	1 (1)	3 (1)	0.44
No change	3 (1)	2 (1)	0.46
Increase			
1–100	13 (4)	9 (2)	0.15
101–199	19 (7)	28 (8)	0.60
200–500	72 (26)	111 (32)	0.12
501–999	48 (17)	61 (17)	0.99
1000–4999	73 (26)	102 (28)	0.46
≥ 5000	51 (18)	39 (11)	0.0095 †
Δ post calcium (pg/ml) ‡	**(n=208)**	**(n=212)**	
Decrease	3 (1)	0 (0)	0.081
No change	3 (1)	3 (2)	0.98
Increase			
1–100	13 (7)	7 (3)	0.18
101–199	17 (8)	11 (5)	0.22
200–500	46 (22)	48 (23)	0.90
501–999	32 (16)	37 (17)	0.57
1000–4999	64 (31)	69 (33)	0.69
≥ 5000	30 (14)	37 (17)	0.40
Δ post meal (% change from basal) §	**(n=238)**	**(n=112)**	
Decrease			
≤ 49%	30 (13)	10 (9)	0.31
50–99	2 (1)	1 (1)	0.96
≥ 100	0 (0)	0 (0)	0.99
No change	7 (3)	9 (8)	0.033 †
Increase			
0–49	96 (40)	58 (52)	0.044 †
50–99	55 (23)	17 (15)	0.087
≥ 100	48 (20)	17 (15)	0.26

* i.v. bolus of 2 UI/kg GIH secretin. Shown is the maximal absolute increase in serum gastrin (in pg/ml) after secretin injection. Literature data prior to 1980 are from [51,68,69,78,79,115,124,132,196,200,232,233,254,255,291,293,296,371,374,393]; literature data from 1980–1989 are from [4,18,20,38,54,73,74,89,91,95,97,99,100,113,125,127,130,134,138,157,169,170,175,178,179,188,218,222,239,240,242,252,258,259,261,272,305,309,315,316,321,322]; literature data from 1990–2005 are from

5,7,8,17,27,35,37,57,61,65,66,70,71,86,94,105,116,131,150,154,172–174,180,202,211,213,241,243,271,314,317,327,328,346,363,367,370,376,392,406,410,412
.

† indicates a significant difference ($p<0.05$).

‡ I.v. infusion of 5 mg/kg/hr calcium or equivalent. Shown is the maximal absolute increase in serum gastrin (in pg/ml) after beginning of calcium infusion. Literature data are from
10,12,13,23,25,46,47,53,54,62,64,69,75,76,78,94,100,107,115,124,139,146,153,175,181,190,196,207–209,214,232,233,235,237,241,255,262,265,267,296,305,318,32
.

§ Standardized meal as described in methods. Shown is the maximal absolute increase in serum gastrin (in pg/ml) after a standard meal. Literature data are from 7,8,10,32,34,47,54,66,69,127,133,153,157,158,190,196,198,215,216,241,294,303,317,340,347,360,371,372,385,389,390.

Table 3.

Distribution of fasting serum gastrin values and evaluation of different proposed criteria for positive results with provocative tests using secretin, calcium and a standardized meal. Data from 537 ZES patients from the literature and 293 ZES patients seen at NIH.

Variable	No. of patients (%)			
	NIH		Literature*	
	All patients	Patients with FSG < 10-fold increase	All patients	Patients with FSG < 10-fold increase
Fasting serum gastrin				
Number of patients	*293*	*190*	*537*	*400*
Fasting serum gastrin (fold normal)				
≤ 1.0	1 (0.3)	1 (0.5)	20 (3.7)	20 (5)
1.1 – 4.9	111 (38)	111 (58)	257 (48)	257 (64)
5.0 – 9.9	78 (27)	78 (41)	123 (23)	123 (31)
≥ 10	103 (35)	0 (0)	137 (25)	0 (0)
Secretin test				
Number of patients	*280*	*181*	*355*	*273*
Change of serum gastrin after secretin				
Δ > 100 pg/ml†	264 (94)	168 (93)	341 (96)	262 (96)
Δ‡ ≥ 110 pg/ml§	262 (93)	166 (92)	341 (96)	262 (96)
Δ ≥ 200 pg/ml**	245 (87)	151 (83)	313 (88)	237 (87)
Δ > 50%†† increase‡‡	237 (84)	155 (86)	286 (81)	229 (84)
Δ >100% increase§§	178 (63)	112 (62)	201 (57)	165 (60)
Maximal serum gastrin value after secretin				
gastrin max. ≥ 186 pg/ml***	280 (100)	180 (100)	353 (99)	271 (99)
gastrin max. ≥ 335 pg/ml†††	261 (93)	162 (89)	345 (97)	263 (96)
Calcium test				
Number of patients	*208*	*142*	*212*	*157*
Change of serum gastrin after calcium				
Δ ≥ 450 pg/ml†	134 (64)	73 (51)	148 (70)	100 (64)
Δ > 395 pg/ml§	139 (67)	77 (54)	159 (75)	110 (70)
Δ > 50% increase‡‡	164 (79)	111 (78)	190 (90)	143 (91)
Δ >100% increase§§	118 (57)	83 (58)	158 (75)	120 (76)
Maximal serum gastrin value after calcium				
gastrin max. ≥ 326 pg/ml†††	201 (97)	135 (95)	195 (92)	141 (90)
Meal test				
Number of patients	*238*	*162*	*112*	*79*
Change of serum gastrin after meal				

Variable	No. of patients (%)			
	NIH		Literature*	
	All patients	Patients with FSG < 10-fold increase	All patients	Patients with FSG < 10-fold increase
< 50% increase‡‡	136 (57)	87 (54)	78 (67)	61 (77)
<100% increase	190 (80)	131 (81)	95 (85)	72 (91)
Maximal serum gastrin value after meal				
gastrin max. > 500 pg/ml†††	175 (74)	100 (62)	76 (68)	45 (57)

*Literature data are from publications listed in Table 2.

†Criterion proposed by Deveney 77

‡The Δ calculated corresponds to the difference between the gastrin value showing the greatest change after stimulation and the basal gastrin value.

§Criterion proposed in publication 78

**Criterion proposed in publication238

††% change (increase or decrease) is calculated as the difference between the gastrin value showing the greatest change after stimulation and the basal gastrin value divided by the basal value and multiplied by 100.

‡‡Criterion proposed in publication 196

§§Criterion proposed in publication 260

***Criterion proposed in publication 301

†††Criterion proposed in publication 219

Table 4.

Effect of different clinical characteristics and tumor features on gastrin levels after secretin, calcium and meal stimulation in 293 Zollinger-Ellison patients seen at NIH [*]

	Δ Secretin (pg/ml)[†]		Δ Calcium (pg/ml)[†]		Δ Meal (%)[*]	
Variable	**Variable present**	**Variable absent**	**Variable present**	**Variable absent**	**Variable present**	**Variable absent**
Age at onset ≤ 40 years						
Median [Range]	831 [0–3000000]	732 [−150–156000]	697 [−166–208000]	935 [−10–75250]	45[§] [−48–2376]	30[§] [−75–8265]
Age at diagnosis ≤ 47 years						
Median [Range]	972 [0–3000000]	686 [−150–47618]	830 [−166–208000]	865 [−10–75250]	43 [−73–675]	30 [−75–8265]
Caucasian race						
Median [Range]	673 [−150–3000000]	1129 [41–158000]	754 [−166–208000]	1332 [24–46000]	38 [−48–2376]	33 [−75–8265]
Duration from onset to diagnosis ≤ 3 years						
Median [Range]	899 [−150–700000]	710 [0–3000000]	919 [−166–208000]	691 [0–75250]	33[§] [−73–346]	48[§] [−75–8265]
Duration from onset to 1st NIH evaluation ≤ 4.9 years						
Median [Range]	686 [−150–3000000]	813 [0–700000]	856 [−166–208000]	709 [0–75250]	35 [−48–675]	40 [−75–8265]
Prior PPI therapy						
Median [Range]	1390 [0–103000]	686 [−150–3000000]	1660 [1–208000]	724 [−166–75250]	53 [−21–2376]	36 [−75–8265]
Duration of prior medical treatment ≤ 1.4 years						
Median [Range]	646[ǂ] [0–103000]	930[ǂ] [−150–3000000]	814 [−10–208000]	959 [−166–53600]	35 [−75–635]	42 [−73–8265]
Prior gastrinoma resection						
Median [Range]	571 [67–158000]	744 [−150–3000000]	501 [460–10144]	850 [−166–208000]	55 [−39–138]	37 [−75–8265]
History of following symptoms at 1st NIH evaluation:						
Pain						
Median [Range]	720 [0–158000]	767 [−150–3000000]	842 [−10–208000]	818 [−166–75250]	34 [−75–8265]	49 [−38–635]
Diarrhea						
Median [Range]	1024[ǂ] [0–700000]	463[ǂ] [−150–3000000]	935 [−166–208000]	691 [−10–25105]	37 [−75–2376]	36 [−45–8265]
Esoph. stricture/ dysphagia						
Median [Range]	1377 [0–101650]	680 [−150–3000000]	3260 [212–46000]	814 [−166–208000]	64[§] [−11–675]	35[§] [−75–8265]
Hx of confirmed ulcer						

	Δ Secretin (pg/ml)†		Δ Calcium (pg/ml)†		Δ Meal (%)*	
Variable	**Variable present**	**Variable absent**	**Variable present**	**Variable absent**	**Variable present**	**Variable absent**
Median [Range]	744 [0–700000]	680 [−150–3000000]	850 [−166–208000]	814 [0–75250]	34 [−48–8265]	53 [−75–635]
Primary lymph node tumor						
Median [Range]	1130 [355–8944]	798 [0–3000000]	2116 [15–8892]	850 [0–208000]	27 [−47–368]	36 [−73–2376]
Tumor extent:						
Primary only						
Median [Range]	715 [102–300000]	1305 [0–700000]	711 [174–9380]	1410 [0–208000]	35 [−45–675]	37 [−73–2376]
Liver metastases						
Median [Range]	904 [0–156000]	744 [−150–3000000]	575 [0–53600]	856 [−166–208000]	22§ [−73–182]	41§ [−75–8265]
Lymph node metastases						
Median [Range]	1485§ [2–700000]	644§ [0–3000000]	1420 [0–208000]	850 [0–75250]	37 [−73–2376]	35 [−45–675]
Size of largest resected tumor:						
≤ 1 cm						
Median [Range]	471‡ [102–26446]	981‡ [−150–3000000]	532§ [15–6803]	1014§ [−166–208000]	51 [−32–259]	34 [−75–8265]
≥ 3 cm						
Median [Range]	1686‡ [0–3000000]	657‡ [−150–700000]	838 [0–75250]	842 [−166–208000]	36 [−73–2376]	38 [−75–8265]

Abbreviations: see table 1; esoph., esophageal; Hx, history.

*For continuous variables, the median value is used to divide the patients into 2 groups.

†Δ secretin, Δ Calcium and Δ meal were calculated as indicated in Methods.

‡P < 0.01

§P < 0.05

Table 5.

Effect of various clinical characteristics, laboratory data and tumor features on serum gastrin levels after secretin stimulation in 355 ZES patients from the literature and 280 patients seen at NIH.

	Δ Secretin (pg/ml)*					
	NIH			Literature†		
Variable‡	Variable Present	Variable Absent	p	Variable Present	Variable Absent	p
Age at evaluation > 48 years						
median [range]	732 [−150–156000]	772 [0–3000000]	0.47	585 [−1–291350]	770 [−25–171000]	0.28
Male gender						
median [range]	644 [0–95500]	1455 [−150–3000000]	0.0075§	600 [−536–4000000]	624 [−1–291350]	0.85
MEN1						
median [range]	1400 [0–3000000]	678 [−150–103000]	0.062	515 [50–291350]	624 [−536–171000]	0.20
Prior acid-reducing surgery						
median [range]	964 [66–700000]	686 [−150–300000]	0.30	680 [61–35500]	594 [−536–4000000]	0.36
BAO > 15 (prior acid-red. surgery)						
Median [Range]	463 [66–31200]	1712 [618–158000]	0.0015§	271 [70–30500]	860 [61–17000]	0.060
MAO > 51 (no prior acid-red. surgery)						
Median [Range]	700 [2–3000000]	580 [0–101650]	0.26	728 [100–46500]	750 [−25–291350]	0.84
Primary tumor size > 1.5 cm (all pts.)						
Median [Range]	793 [0–103000]	790 [41–3000000]	0.92	653 [181–38000]	590 [141–5100]	0.59
Primary tumor size ≥ 3 cm (all pts.)						
Median [Range]	667 [0–56527]	830 [41–3000000]	0.82	653 [181–38000]	590 [141–9000]	0.76
Primary localization pancreas						
Median [Range]	720 [0–158000]	830 [88–3000000]	0.24	600 [40–291350]	700 [−25–85000]	0.94
Primary localization duodenum						
Median [Range]	798 [88–3000000]	831 [0–56527]	0.96	683 [−25–291350]	600 [45–8198]	0.68
Localized disease**						
Median [Range]	732 [−150–3000000]	1129 [0–156000]	0.97	536 [−25–85000]	1132 [−536–291350]	0.12

Abbreviations: See Table 1. Pts., patients; mets., metastases.

*'Δ secretin' corresponds to the maximal absolute change in serum gastrin levels (expressed in pg/ml) after injection of 2 units of secretin.

†Literature data are from publications listed in Table 2.

‡For continuous variables, the median of the total population (NIH+literature) is used to divide the patients into 2 groups.

§indicates a significance difference ($p<0.05$)

** 'Localized disease' includes all patients without evidence for liver or other distant metastases.

Table 6.

Effect of various clinical characteristics, laboratory data and tumor features on serum gastrin levels calcium stimulation in 208 patients seen at NIH and 212 ZES patients from the literature.

	Δ Calcium (pg/ml)*					
	NIH			Literature†		
Variable‡	Variable Present	Variable Absent	p	Variable Present	Variable Absent	p
Age at evaluation > 48 years						
median [range]	865 [−10–75250]	835 [−166–208000]	0.78	1000 [0–116047]]	1000 [0–95000]	0.41
Male gender						
median [range]	1453 [−10–25105]	3825 [−166–208000]	0.016§	912 [0–95000]	1121 [0–116047]	0.15
MEN1						
median [range]	1222 [−166–17590]	774 [−10–208000]	0.25	980 [48–116047]	980 [0–95000]	0.66
Prior acid-reducing surgery						
median [range]	1230 [0–53600]	826 [−166–208000]	0.24	1115 [68–92140]	980 [0–168000]	0.33
BAO > 15 (prior acid-reducing surgery)						
Median [Range]	535 [0–53600]	4420 [705–25105]	0.0013§	975 [68–22724]	912 [145–92140]	0.74
MAO > 51 (no prior acid-reducing surgery)						
Median [Range]	850 [−166–208000]	701 [1–46000]	0.92	1595 [0–168000]	980 [0–7993]	0.15
Primary tumor size > 1.5 cm (all pts.)						
Median [Range]	1182 [0–208000]	697 [15–17590]	0.17	No Data**	No Data	
Primary tumor size ≥ 3 cm (all pts.)						
Median [Range]	838 [0–75250]	888 [1–208000]	0.58	No Data	No Data	
Primary localization pancreas						
Median [Range]	958 [0–75250]	814 [1–208000]	0.79	691 [48–29000]	1170 [0–95000]	0.80
Primary localization duodenum						
Median [Range]	698 [1–208000]	1035 [0–75250]	0.60	1170 [0–9890]	691 [48–95000]	0.85
Localized disease††						
Median [Range]	850 [−166–208000]	602 [0–53600]	0.28	1122 [0–28650]	1235 [0–95000]	0.87

Abbreviations: See Table 1. Pts., patients; mts., metastases.

*'Δ Calcium' corresponds to the maximal absolute change in serum gastrin levels (expressed in pg/ml) after infusion of 5 mg/kg/hr. calcium for 3 hours. Indicated are the median and the range for each group of patients.

†Literature data are from publications listed in Table 2.

‡For continuous variables, the median of the total population (NIH+literature) is used to divide the patients into 2 groups.

§ indicates a significant difference ($p<0.05$).

** 'No Data' indicates that information was available on less than 10 patients.

†† 'Localized disease' includes all patients without evidence for liver or other distant metastases.

Table 7.

Effect of various clinical characteristics, laboratory data and tumor features on serum gastrin levels after a standard test meal in 208 patients seen at NIH and 112 ZES patients from the literature.

	Δ Meal (%)*					
	NIH			Literature†		
Variable‡	Variable Present	Variable Absent	p	Variable Present	Variable Absent	p
Age at evaluation > 48 years						
median [range]	32 [−75–8265]	42 [−48–675]	0.17	38 [−10–155]	31 [−90–900]	0.45
Male gender						
median [range]	33 [−75–8265]	44 [−73–675]	0.18	24 [−25–173]	40 [−90–900]	0.40
MEN1						
median [range]	59 [−75–186]	34 [−48–8265]	0.019§	38 [−90–191]	37 [−38–900]	0.99
Prior acid-reducing surgery						
median [range]	24 [−42–8265]	41 [−75–2376]	0.17	50 [−25–284]	36 [−90–900]	0.14
BAO > 15 (prior acid-reducing surgery)						
Median [Range]	24 [−40–8265]	28 [−42–83]	0.67	75 [−25–284]	50 [27–191]	>0.99
MAO > 51 (no prior acid-reducing surgery)						
Median [Range]	46 [−75–675]	26 [−45–635]	0.067	10 [−10–900]	37 [−7–153]	0.43
Primary tumor size > 1.5 cm (all pts.)						
Median [Range]	28 [−75–675]	38 [−73–2376]	0.26	No Data**	No Data	
Primary tumor size ≥ 3 cm (all pts.)						
Median [Range]	22 [−75–675]	36 [−75–2376]	0.30	No Data	No Data	
Primary localization pancreas						
Median [Range]	26 [−75–190]	39 [−73–2376]	0.054	58 [−25–284]	46 [−7–900]	0.89
Primary localization duodenum						
Median [Range]	48 [−73–2376]	26 [−75–675]	0.0081§	82 [−7–223]	55 [−25–900]	0.95
Localized disease††						
Median [Range]	39 [−75–8265]	26 [−73–182]	0.088	49 [−38–900]	34 [−25–284]	0.92

Abbreviations: See Table 1. Pts., patients; mts., metastases.

*‘Δ meal (%)was calculated as described in Methods.

†Literature data are from publications listed in Table 2.

‡For continuous variables, the median of the total population (NIH+literature) is used to divide the patients into 2 groups.

§* indicates a significant difference ($p<0.05$).

**‘No Data’ indicates that information was available on less than 10 patients.

††‘Localized disease’ includes all patients without evidence for liver or other distant metastases.

Table 8.

Influence of clinical variables, acid secretion data and tumor features on the results of the secretin stimulation test in 280 ZES-patients seen at NIH and 355 patients from the literature.

	Variable present*					
	NIH			Literature†		
Variable‡	Δ Secretin ≥ 200	Δ secretin < 200	p	Δ Secretin ≥ 200	Δ secretin < 200	p
Age ≥ 48 years	131 (53)	15 (43)	0.24	131 (50)	23 (62)	0.15
Male gender	137 (56)	22 (55)	0.97	156 (60)	8 (19)	<0.0001§
MEN1 present	71 (29)	12 (30)	0.31	56 (18)	6 (9.5)	0.50
Previous acid-reducing surgery	38 (16)	4 (10)	0.62	57 (18)	19 (51)	<0.0001§
BAO > 35 (no acid-reducing surgery)	120 (60)	17 (52)	0.23	67 (49)	9 (47)	0.92
MAO > 51 (no acid-reducing surgery)	110 (63)	18 (58)	0.47	38 (45)	4 (40)	>0.99
Primary size > 1.5 cm (all patients)	71 (39)	13 (65)	0.027§	21 (44)	1 (20)	0.39
Primary size > 1.3 cm (no liver metastases)	63 (42)	4 (44)	>0.99	22 (49)	0 (0)	0.11
Primary size ≤ 1 cm (all patients)	90 (50)	7 (35)	0.2	24 (50)	8 (44)	0.69
Primary size ≤ 1 cm (no liver metastases)	78 (52)	5 (55)	>0.99	28 (56)	4 (22)	0.10
Primary size ≥ 3 cm (all patients)	40 (22)	9 (35)	0.023§	14 (29)	7 (39)	0.42
Primary size ≥ 3 cm (no liver metastases)	24 (26)	3 (25)	0.18	11 (24)	13 (65)	0.0018§
Pancreatic primary tumor	65 (28)	15 (37)	0.17	61 (47)	8 (44)	0.84
Duodenal primary tumor	99 (40)	8 (20)	0.0017§	50 (38)	7 (39)	0.97
Other primary tumor	32 (13)	3 (7.5)	0.59	22 (17)	4 (22)	0.52
Localized disease	212 (86)	26 (72)	0.026§	111 (74)	13 (65)	0.37

Abbreviations: see table 1.

*Indicated is the number and percentage of patients with the indicated variable present, subdivided according to the secretin stimulation test. Data for literature patients is derived from the publications cited in Figure 1. The total number of patients in each group can be calculated using the number and percentage values.

†Literature data are from publications listed in Table 2.

‡For continuous variables, the median of the total population (NIH + Literature) is used to divide patients into 2 groups.

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§indicates a significant difference ($p<0.05$).

Table 9.

Comparison of results with four different doses of secretin (synthetic or GIH) used for provocative testing using multiple proposed criteria for positive tests for ZES patients from the literature.

Secretin dose	No. of patients (%)							
	1 unit/kg*		75 units†		2 units/kg‡		3 units/kg§	
	All patients	FSG < 10-fold increase	All patients	FSG < 10-fold increase	All patients	FSG < 10-fold increase	All patients	FSG < 10-fold increase
Number of patients	*116*	*91*	*28*	*19*	355	*273*	*42*	*14*
Change of serum gastrin after secretin**								
Δ > 100 pg/ml	92 (79)	68 (75)	27 (96)	18 (95)	343 (97)	264 (97)	30 (71)	8 (57)
Δ ≥ 110 pg/ml	92 (79)	68 (75)	25 (89)	16 (84)	341 (96)	262 (96)	30 (71)	8 (57)
Δ ≥ 200 pg/ml	81 (70)	58 (64)	20 (71)	11 (58)	313 (88)	237 (87)	28 (66)	5 (36)
Δ > 50% increase	89 (76)	69 (76)	26 (93)	17 (89)	286 (81)	229 (84)	19 (63)	10 (71)
Δ >100% increase	59 (51)	46 (51)	25 (89)	16 (84)	201 (57)	165 (60)	15 (50)	8 (57)
Max. serum gastrin value after secretin								
Gastrin max. ≥ 186 pg/ml	97 (84)	72 (79)	28 (100)	19 (100)	353 (99)	271 (99)	41 (98)	13 (93)
Gastrin max. ≥ 335 pg/ml	93 (80)	68 (75)	25 (89)	16 (84)	345 (97)	263 (96)	34 (81)	6 (43)

*Data are from 46,75,82,101,157,189–191,193,196,198,215,303,307,308,340,344,352,389.

†Data are from 13,28,64,69,135,212,313,373

‡Data are from publications listed in table 2

§Data are from 19,48,50,55,146–149,229,380,404,405

**Δ secretin corresponds to the absolute (pg/ml) or relative (%) change in serum gastrin concentration after secretin injection.

Table 10.

Fasting serum gastrin distribution and evaluation of different proposed criteria for positive results for provocative tests using secretin and calcium in 462 patients from the literature without ZES.

	No. of patients (%)*	
	Literature non-ZES patients without achlorhydria†	**Literature non-ZES patients with achlorhydria‡**
Fasting serum gastrin		
Number of patients	*147*	*25*
Fasting serum gastrin (fold normal)		
≤ 1.0	76 (52)	0 (0)
1.1 – 4.9	66 (45)	5 (20)
5.0 – 9.9	4 (3)	10 (40)
≥ 10	1 (1)	10 (10)
Secretin test		
Number of patients (Δ pg/ml)	*462*	*27*
Number of patients (Δ %)	*223*	*27*
Number of patients (absolute increase)	*134*	*27*
Change of serum gastrin after secretin		
Δ > 100 pg/ml§	1 (0.22)	9 (33)
Δ** ≥ 110 pg/ml††	0 (0)	9 (33)
Δ ≥ 200 pg/ml‡‡	0 (0)	5 (18)
Δ > 50%§§ increase***	16 (7)	2 (7)
Δ >100% increase†††	3 (1)	0
Maximal serum gastrin value after secretin		
gastrin max. ≥ 186 pg/ml‡‡‡	17 (13)	27 (100)
gastrin max. ≥ 335 pg/ml§§§	5 (4)	26 (96)
Calcium test		
Number of patients (Δ pg/ml)	*100*	
Number of patients (Δ %)	*105*	
Number of patients (absolute increase)	*59*	
Change of serum gastrin after calcium		
Δ > 450 pg/ml§	0 (0)	
Δ ≥ 395 pg/ml	0 (0)	
> 50% increase	17 (17)	
>100% increase	10 (9.5)	
Maximal serum gastrin value after calcium		
gastrin max. ≥ 326 pg/ml	1 (1.7)	

Abbreviations: see table 1.

† Patients with antral G-cell hyperplasia, moderate hypochlorhydria, peptic ulcer disease and patients with normal gastric function were included. Data are from [7,8,28,42,69,78,81,99,157,189,192,193,196,219,229,255,295,307,318,331,344,380]

‡ Data are from [42,98,141,192,219]

§ Criterion proposed by Deveney [77]

** The Δ calculated corresponds to the difference between the gastrin value showing the greatest change after stimulation and the basal gastrin value. Data available for 437 patients.

†† Criterion proposed in publication [78]

‡‡ Criterion proposed in publication [238]

§§§§ % change (increase or decrease) is calculated as the difference between the gastrin value showing the greatest change after stimulation and the basal gastrin value divided by the basal value and multiplied by 100.

*** Criterion proposed in publication [196]

††† Criterion proposed in publication [260]

‡‡‡ Criterion proposed in publication [301]

§§§ Criterion proposed in publication [219]

Table 11.

Comparison of the sensitivity and specificity of different criteria for positive results with provocative tests using secretin in 1097 NIH and literature patients.

	No. of patients (%)				
	NIH+Literature ZES-patients*		Literature non-ZES patients†	Sensitivity‡ (%)	Specificity‡ (%)
Change of serum gastrin after secretin	All patients	Patients with FSG < 10-fold increase§	Patients without achlorhydria only		
Number of patients	*635*	*453*	*462*		
Δ > 100 pg/ml	605 (95)	430 (95)***	1 (0.22)	95	99.8
Δ** ≥ 110 pg/ml	603 (95)	428 (94)***	0 (0)	94	100
Δ ≥ 200 pg/ml	558 (88)	388 (87)	0 (0)	87	100
Δ ≥ 190 pg/ml	562 (89)	391 (86)	0 (0)	86	100
Δ ≥ 180 pg/ml	572 (90)	400 (88)	0 (0)	88	100
Δ ≥ 170 pg/ml	576 (91)	403 (89)	0 (0)	89	100
Δ ≥ 160 pg/ml	579 (91)	406 (90)	0 (0)	90	100
Δ ≥ 150 pg/ml	582 (92)	408 (90)	0 (0)	90	100
Δ ≥ 140 pg/ml	588 (93)	414 (91)*	0 (0)	91	100
Δ ≥ 130 pg/ml	591 (93)	417 (92)**	0 (0)	92	100
Δ ≥ 120 pg/ml	600 (94)	425 (94)***	0 (0)	94	100

*Data for literature patients are from publications listed in table 2.

†Data are from publications listed in Table 12.

‡Sensitivity and specificity calculated for the clinically relevant group of patients with a fasting serum gastrin < 10-fold increase.

§*p<0.05, **p<0.01 and *** p<0.003 compared to sensitivity of Δ ≥ 200 pg/ml criterion.

**The Δ calculated corresponds to the absolute change in serum gastrin above basal after stimulation with secretin.

Table 12.

Comparison of provocative test results using secretin, calcium or a standard meal in ZES patients from large studies, the remaining literature and NIH using different criteria for positive testing. Indicated are the percentage of all patients and the percentage of patients with FSG < 10-fold increase (in brackets) with positive tests at a given criterion. The patients analyzed in the individual studies indicated were excluded of the analysis of literature data.

Secretin test	*Deveney*[*] *1977*	*Mc Callum 1979*	*Stabile 1980*	*Feurle 1982*	*Malegelada 1983*	*Richardson 1985*	*Corletto 1993*	*Imamura 1994*	*Zimmer 1996*	*Literature*[*]	*NIH*
	(n=10)	*(n=15)*	*(n=21)*	*(n=16)*	*(n=10)*	*(n=22)*	*(n=13)*	*(n=11)*	*(n=10)*	*(n=227)*	*(n=309)*
Reference	78	232	341	100	218	315	66	150	412		
Δ≥110 pg/ml †	100% (100%)	100% (100%)	95% (100%)	94% (93%)	90% (90%)	91% (89%)	100% (100%)	100% (100%)	100% (100%)	96% (96%)	93% (92%)
Δ≥200 pg/ml ‡	80% (80%)	80% (70%)	95% (100%)	87% (86%)	90% (90%)	86% (83%)	100% (100%)	91% (89%)	100% (100%)	87% (85%)	87% (83%)
> 50% increase §	80% (80%)	87% (100%)	81% (94%)	87% (86%)	70% (70%)	77% (78%)	100% (100%)	45% (44%)	70% (70%)	81% (85%)	84% (86%)
Calcium test	*Morrow*[**] *1975*	*Deveney 1977*	*Lamers 1977*	*McCallum 1979*	*Stabile 1980*	*Basso 1981*	*Romanus 1983*	*Literature*[**]	*NIH*		
	(n=14)	*(n=12)*	*(n=15)*	*(n=13)*	*(n=19)*	*(n=11)*	*(n=13)*	*(n=113)*	*(n=208)*		
Reference	262	78	196	232	341	23	318				
Δ≥395 pg/ml ‡‡	64% (58%)	75% (75%)	87% (89%)	62% (44%)	74% (67%)	55% (50%)	92% (88%)	76% (72%)	67% (54%)		
> 50% increase §	86% (83%)	92% (92%)	87% (89%)	100% (100%)	100% (100%)	100% (100%)	100% (100%)	85% (87%)	79% (78%)		
Meal test	*Creutzfeld*[††] *1975*	*Strauss 1975*	*Thompson 1975*	*Lamers 1977*	*Malagelada 1978*	*Jansen 1982*	*Literature*[**]	*NIH*			
	(n=9)	*(n=7)*	*(n=11)*	*(n=9)*	*(n=6)*	*(n=7)*	*(n=63)*	*(n=208)*			
Reference	69	347	360	196	216	157					
<50% increase ‡‡	22% (40%)	86% (86%)	18% (20%)	89% (87%)	33% (67%)	100% (100%)	81% (82%)	57% (54%)			
< 100% increase §	56% (40%)	86% (86%)	54% (80%)	100% (100%)	50% (100%)	100% (100%)	94% (96%)	80% (81%)			

Abbreviations: see Table 1

[*] Studies including ≥ 10 patients are listed individually, smaller studies are grouped under “Literature”. Literature data are from publications listed in Table 2.

† Criterion proposed in publication [77]

‡ Criterion proposed in publication [238]

§ Criterion proposed in publication [196]

Abbreviations: see Table 1

** Studies including ≥ 10 patients are listed individually, smaller studies are grouped under "Literature". Literature data are from publications listed in Table 2.

†† The 6 largest studies are listed individually, smaller studies are grouped under "Literature". Literature data are from publications listed in Table 2.

‡‡ Criterion proposed in publication [78]

Table 13.

Key findings of an analysis of gastrin provocative tests in NIH and literature ZES patients.

A. Secretin provocative tests show:

1. An increase in serum gastrin post secretin (Δ secretin) in 99% of all patients and 99% of patients with a fasting serum gastrin (FSG) <10-fold increased.

2. In 453 ZES patients with FSG <10-fold increased, the sensitivity of proposed criteria: Δ≥110 (94%), Δ≥120 (94%), Δ≥200 pg/ml (87%), Δ>50% (85%), Δ>100% (61%).

3. In 462 non-ZES patients without achlorhydria, the specificity of these proposed criteria was: Δ≥110 (100%), Δ≥120 (100%), Δ≥200 (100%), Δ>50% (93%), Δ>100% (99%).

4. A new criterion of Δ≥120 pg/ml was found to have the highest sensitivity (94%) and specificity (100%) and should be used in the future.

5. Δ secretin significantly correlates with BAO but not MAO as well as with some clinical findings reflecting hyperchlorhydria (diarrhea, duration of medical treatment).

6. Δ secretin correlates with tumor size and disease extent.

B. Calcium provocative tests show:

1. An increase in serum gastrin post calcium (Δ calcium) in 98% of all patients and 97% of patients with FSG <10-fold increased.

2. In 299 ZES patients with FSG<10-fold increased, the sensitivity of proposed criteria was: Δ≥450 (58%), Δ≥395 (62%), Δ>50% (85%), Δ>100% (68%).

3. In 105 non-ZES patients without achlorhydria, the specificity of these proposed criteria was: Δ≥450 (100%), Δ≥395 (100%), Δ>50% (83%), Δ>100% (90%).

4. A Δ ≥395 pg/ml gives maximal sensitivity (62%) with 100% specificity and should be used as criterion for a positive test.

5. The calcium test has a significantly lower sensitivity than the secretin test (62% vs. 94%) and has greater side effects. Therefore it should not be used as first-line provocative test.

6. Is positive (Δ≥395 pg/ml) in 38–50% of patients with a negative secretin test.

7. Δ calcium significantly correlates with BAO but not MAO values. There is no significant correlation with clinical symptoms or tumor characteristics.

Meal provocative tests show:

1. An increase in serum gastrin post meal (Δ meal) in 84% of all patients and 85% of patients with a FSG <10-fold increased.

2. In 241 ZES patients with a FSG <10-fold increased: a) 61% have a <50% Δ meal. b) 16% have Δ meal ≥100% increase overlapping with the response in antral syndromes.

3. Because of this overlap, the standard meal test is not clinically useful in the diagnosis of ZES.

4. Δ meal test correlates with some clinical findings (time to diagnosis, age of onset, presence of MEN1, heartburn, esophageal disease) and with tumor location.