Pseudo-Zollinger-Ellison Syndrome

Hypergastrinemia, Hyperchlorhydria without Tumor

STANLEY R. FRIESEN, M.D., PH.D., TATSUO TOMITA, M.D., PH.D.

From the Departments of Surgery and Pathology and Oncology, University of Kansas Medical Center and College of Health Sciences, Kansas City, Kansas

The purpose of the investigation was to detect ulcer patients having nontumorous hypergastrinemic hyperchlorhydria and to diagnostically differentiate this pseudo-Zollinger-Ellison syndrome from neurogenic duodenal ulcer disease and pancreatic gastrinomas. Nine patients having clinical, radiologic and humoral findings simulating the Zollinger-Ellison syndrome or severe duodenal ulcer disease were studied by physiologic provocative testing. The patients, not having pancreaticoduodenal gastrinomas, had an antral mucosal source of their moderate hypergastrinemia even after vagotomy with drainage, which was eliminated in eight patients treated by surgical antrectomy, resulting in normal serum gastrin concentrations. The pseudo-Zollinger-Ellison syndrome is, thus, characterized physiologically by an exaggerated gastrin response to meals, no response to secretin stimulation and pathologically by hyperfunctioning hyperplastic G cells of the antrum. The clinical, physiologic, pathologic and surgical features were integrated for accurate diagnosis and treatment.

THERE ARE PATIENTS who exhibit the clinical features of the Zollinger-Ellison syndrome (ZES), including the usually diagnostic elevated serum gastrin (SG) concentration, who do not have gastrinoma tumors of the pancreas or duodenum. Such patients have an antral mucosal source of their hypergastrinemia. The classic Zollinger-Ellison syndrome, as originally described in 1955, consists of a triad of intractible ulceration, marked gastric acid hypersecretion and pancreatic non-Beta islet cell tumor[1]; by definition, the similar clinical picture associated with an antral mucosal origin without tumor cannot be accurately termed the Zollinger-Ellison syndrome, hence the proposed clinical designation of pseudo-Zollinger-Ellison syndrome (Ps-ZES).[2] In the past this clinical state was recognized and considered to be an ulcerogenic syndrome representing an intermediary stage between the common duodenal ulcer diathesis of neurogenic origin and the typical ZES of humoral origin from pancreaticoduodenal gastrinomas.[3] More recently, a physiologic designation has been ascribed to the same clinical picture with hypergastrinemia of antral origin as nontumorous hypergastrinemic hyperchlorhydria (NTHH).[4] It was postulated that there is an "over-activity of the gastrin-secreting cells of the gastrointestinal mucosa." Moreover, from a pathologic viewpoint, the antral source of hypergastrinemia has been reported as one of two types of the Zollinger-Ellison syndrome, namely, antral G cell hyperplasia (AGCH), as contrasted to tumor gastrinomas, based on immunocytochemical techniques.[5,6] Whatever the designation, in such patients with clinical and humoral findings simulating ZES, there is an inappropriate release of antral mucosal gastrin in the presence of gastric hyperchlorhydria, a concept based on physiologic results of provocative testing (Fig. 1).[4]

The incidence of this entity is unknown, but with refinements of diagnostic procedures, including provocative testing, its recognition is increasing as awareness of its possibility is appreciated. Just as the ZES was considered to be extremely rare at the time of its original description, only to become more universally recognized, the early reports of Ps-ZES, NTHH and AGCH were sporadic and anecdotal with minimal integration of their component features.[2-12] In 1972, Berson and Yalow described four patients with NTHH[9]; more recently, in the same institution, the entity has been physiologically delineated in 30 of 213 hypersecretory patients, as compared with 48 ZES patients in that group.[4] This apparent increase in in-

Presented at the Annual Meeting of the American Surgical Association, Chicago, Illinois, April 22-24, 1981.

Supported in part by National Institutes of Health grant RR-828 (General Clinical Research Centers Branch) and by the McGreevy, Morales, Foley, Miller, Plummer and Svoboda Research Funds.

Reprint requests: Stanley R. Friesen, M.D., Department of Surgery, University of Kansas Medical Center and College of Health Sciences, Kansas City, Kansas 66103.

0003-4932/81/1000/0481 $01.15

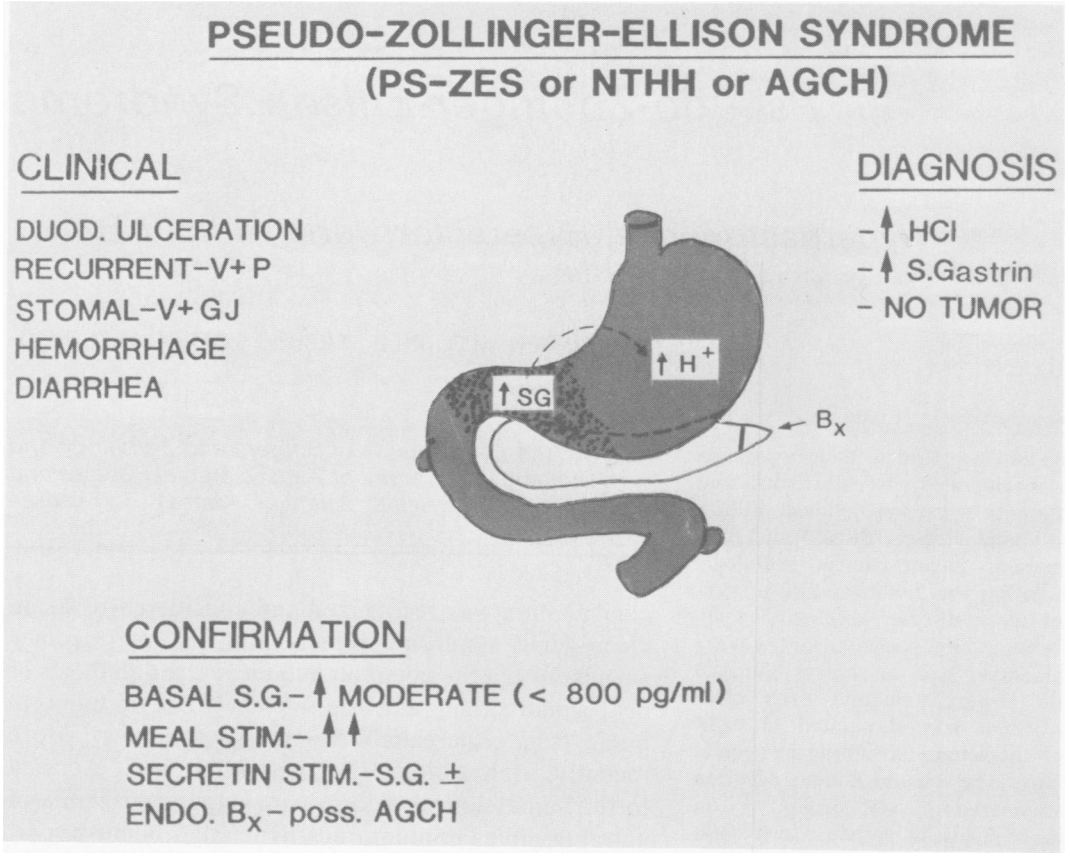

FIG. 1. Clinical diagram illustrating the diagnostic, physiologic and pathologic characteristics of Pseudo-Zollinger-Ellison Syndrome.

cidence of NTHH is accountable to the development of refinements in diagnostic procedures in an institution which is a widely recognized referral center.

The clinical significance of differentiating between the various causes of hypergastrinism in ulcer patients becomes obvious when it is realized that the management of patients with ZES differs from that of Ps-ZES. Patients having the clinical features of ZES are being seen in whom no gastrinoma is found surgically or radiologically; some patients in those situations are subjected to total gastrectomy when antrectomy with vagotomy might suffice, if it were known preoperatively that the pathogenesis was in the antrum. On the other hand, patients in whom current radiologic techniques have failed to demonstrate a gastrinoma have been treated by long-term cimetidine administration without an opportunity for surgical clarification of the correct diagnosis and concomitant excisional treatment of the specific sources of the hypergastrinemia and hyperchlorhydria. Diagnostic differentiation between ZES and Ps-ZES by means of provocative testing is especially important in ulcer patients with moderately elevated basal serum gastrin concentrations of less than 1000 pg/ml without evidence of metastases; it is precisely this clinical situation in which serum gastrin responses to provocative stimuli provide the basis for diagnostic discrimination.

Furthermore, diagnostic differentiation between ordinary neurogenic duodenal ulcer and NTHH with inappropriate antral gastrin release is also therapeutically important, when it is realized that the antrum is the major factor in the generally accepted 10% difference in the incidence of recurrent ulcer after vagotomy with pyloroplasty (10.4%) and vagotomy with antrectomy (0%) for duodenal ulcer disease.[13] Recurrence of ulceration after vagotomy without antrectomy is due to incomplete vagotomy or to overlooked antral or pancreatic sources of hypergastrinemia. While cimetidine is, clinically, an excellent treatment of the hyperchlorhydria in all three ulcer conditions, it is only palliative and does not deal directly with the neurogenic influence or either of the humoral causes of the altered physiology. The protective value of cimetidine in allowing preoperative diagnostic evaluation and discrimination for appropriate surgical therapy of any of the ulcerogenic conditions has been demonstrated.[14–17]

Methods of Diagnostic Discrimination (Figs. 2 and 3)

Basal Serum Gastrin Concentration

The basal fasting levels of circulating serum gastrin provide in themselves some discriminative value between ZES and Ps-ZES and DU, but there is an over-

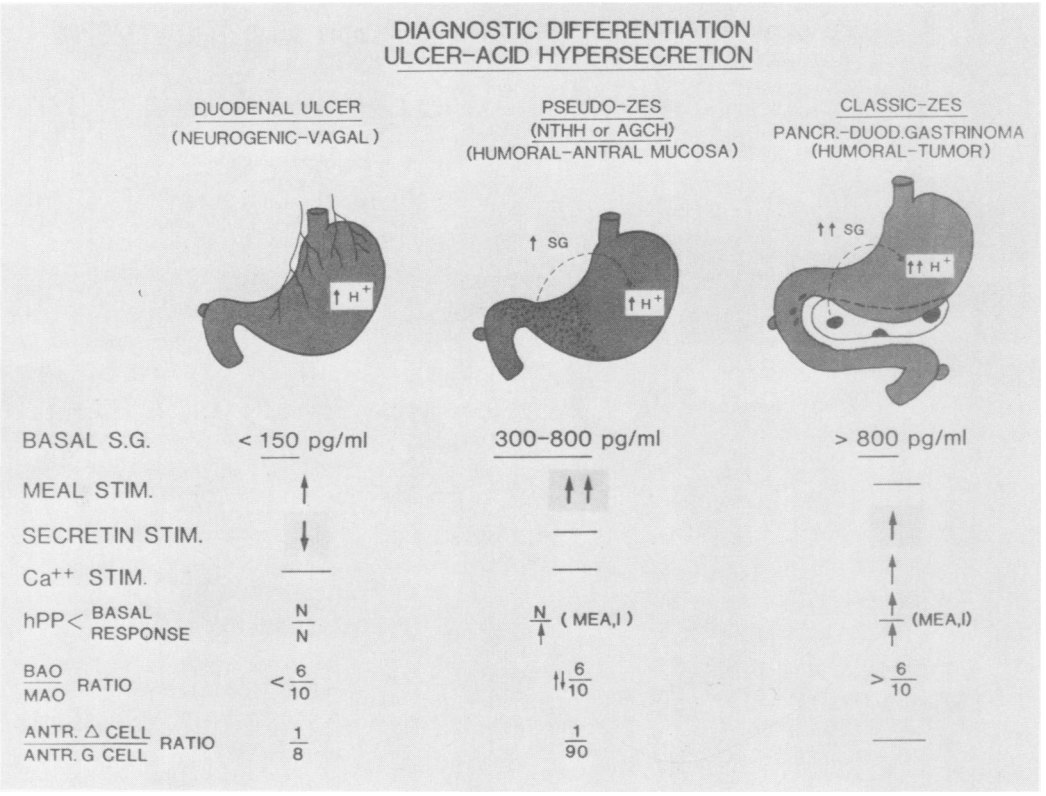

FIG. 2. Schema of the diagnostic differentiation by means of provocative testing between the neurogenic duodenal ulcer diathesis, the Pseudo-Zollinger-Ellison Syndrome and the classic Zollinger-Ellison Syndrome with pancreatico-duodenal gastrinoma(s).

lap of levels particularly in the former two diagnoses. While the SG levels tend to be high in ZES (range: 300 to >2000 pg/ml), all reports of basal SG concentrations in Ps-ZES patients have been under 1000 pg/ml[4] with one exception.[8] Generally the broadest range of SG concentrations in Ps-ZES is from 200 to 800 pg/ml, the usual being 200–600 pg/ml. The range in normal patients in the author's institution is 66–174 pg/ml (mean: 97 pg/ml) and in patients with DU the mean is 107 pg/ml; the mean for DU patients is generally reported as well under 125 pg/ml and as low as 15.7 and 57 pg/ml.[18,19] The method used for radioimmunoassay of gastrin concentration in the serum in this study was by the Beckton-Dickinson® kit.

Stimulation Tests

Provocative tests demonstrate that the stimuli for gastrin release from tumor differ from those for release of gastrin from the antral mucosa. A standard test meal (STM)* will usually produce a rise in circulating serum gastrin in normal persons (mean maximal increase of 120%), in patients with DU (190% rise), and in patients with NTHH (Ps-ZES) (300% rise); in patients with ZES the rise in SG is minimal, if at all (40% mean maximal rise over basal values).[4] Blood for serum gastrin response to the STM in this study was drawn prior to the meal and 15, 30, 45, 60, 90, 120 and 180 minutes after the stimulus.

The secretin stimulation test is even more discriminatory: in "normals" and DU patients either no increase in SG occurs, or, more commonly, a decrease in SG follows stimulation[20], in NTHH (Ps-ZES) patients no significant change in SG levels is demonstrated,[4] while in proven ZES patients, a paradoxical hyperresponse follows (usually an increase over 110 pg/ml)[19] or greater.[4,20] The response is dose-related with greater discrimination using 4 U Boots secretin/kg body weight by intravenous push, rather than with the dose of 1 or 2 units/kg body weight.[4] In the present study, Boots secretin, 2 units/kg/intravenous push was used and blood for serum gastrin response was drawn at zero time and five, ten, 15, 20, 30, 45, and 60 minutes after the stimulus.

The calcium stimulation test by intravenous challenge or by slow infusion,[21] produces similar changes in SG concentrations but is less reliable because it may cause a 30% rise of SG in some patients with DU,[4] no significant change in SG in NTHH (Ps-ZES) is observed, but a marked rise occurs in gastrinoma patients (350% mean maximal rise).[4] In the present study, blood for serum calcium levels and for serum

* The standard test meal (STM) is the same as that used for the response of human pancreatic polypeptide (hPP) in the plasma to a meal, namely a standard high protein breakfast of three medium eggs, two slices of bacon, two slices of toast and eight ounces of 2% milk, which contains a total of 34.5 g of protein, 26.6 g of fat and 41.1 g of carbohydrate.

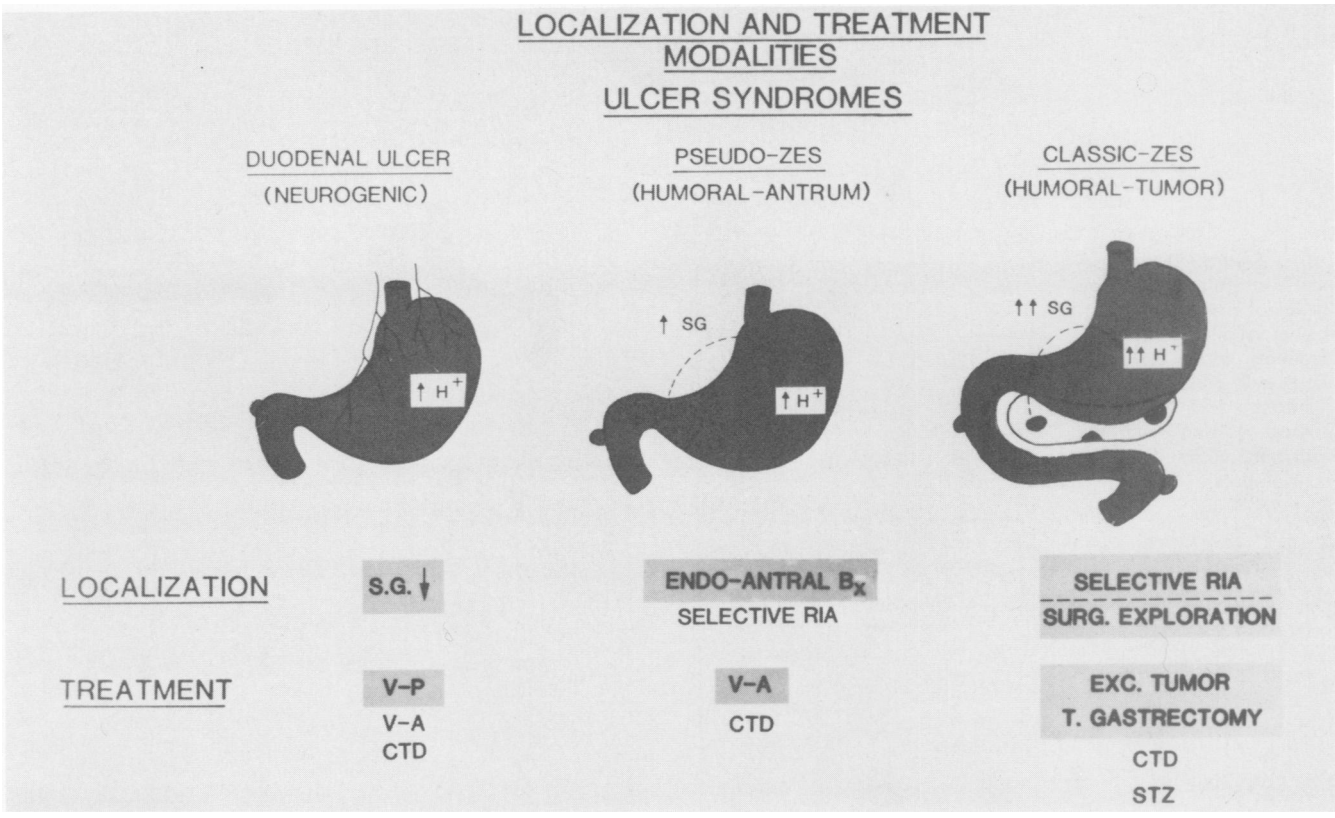

FIG. 3. Schema of the localization techniques and therapeutic modalities for discrimination between the duodenal ulcer diathesis, the Pseudo-Zollinger-Ellison Syndrome and pancreatico-duodenal gastrinomas.

gastrin response to calcium stimulation by infusion (4 mg/kg/hr intravenously for three hours) was drawn at zero time and at 30 minute intervals for three hours.

The basal concentrations of plasma hPP and its response after a STM is somewhat discriminatory in ulcer patients suspected of conforming to a genetic pathogenesis of multiple endocrine adenopathy (MEA, type I), Wermer's Syndrome.[2] Patients with the MEA,I trait as determined by the presence of AGCH, have a normal basal hPP and an exaggerated (>4 × basal) plasma hPP response to a meal; patients with ZES in MEA,I have approximately a 50% incidence of having an elevated basal hPP concentration.[22,23] In this present study, blood for plasma hPP assay[24] was drawn before and at 30, 60, 120 and 180 minutes after the STM.

Gastric acid secretory output is not significantly discriminatory for diagnosis, unless the ratio of basal to maximally stimulated output exceeds 6:10, often observed in ZES patients. Stimulation for maximal acid secretory concentration or hourly output in this study was by pentagastrin, histalog or by insulin hypoglycemia.

Pathologic Differentiation

Further confirmatory discrimination is possible by means of pathologic studies, namely cytochemical analyses of G cell population and degree of granulation in mucosal biopsies obtained endoscopically[3] conveniently at the time of search for possible duodenal gastrinomas. The preoperative diagnosis of gastrin-secreting tumor or AGCH is most frequently established on physiologic grounds but confirmation on the basis of structural (cytologic) evidence is also desirable; hence endoscopic biopsies for antral G cell characteristics. Using cytochemical techniques on the antral mucosa, quantitatively by television image reproduction, Polak et al. were able to separate patients with tumors from those of the antral origin; antral G cell hyperplasia was described with G cell populations over 30 times that seen in normal or gastrinoma patients.[5] Four additional patients had AGCH as demonstrated by immunofluorescent techniques on paraffin fixed sections. Marked compactions of antral G cells have been described in patients with antral hypergastrinemia; only four gastrin tumors of

the pyloric antrum have been observed[16,25–27]; one was associated with a pancreatic gastrinoma[16] and another with islet nesidioblastosis.[25] Four gastrin tumors of the gastric corpus have been reported,[28–31] two were associated with AGCH.[30,31]

Antral G cell counts compared with D cell (somatostatin-secreting cell) populations have been derived as ratios which also discriminate between patients with DU and AGCH.[32] The gastrin cell count relative to the D cell count in patients with DU was 242 to 30/sq mm, a G to D cell ratio of 8:1, while in patients with AGCH they were 2720 to 30, a G:D ratio of 90:1.

In the patients reported in the present study, antral mucosa was obtained by endoscopic and/or surgical biopsy. The endoscopic biopsy specimen was fixed in cold 2% glutaraldehyde and antrectomy specimen was fixed in 10% buffered formaldehyde and/or Bouin's solution, in preparation for immunoperoxidase studies of G cell populations. Pancreatic biopsies to rule out islet abnormalities were surgically obtained by amputation of the distal tip of the pancreas, fixed in Bouin's fluid and treated similarly. The deparaffinized sections were processed for indirect peroxidase conjugate method (A) with the use of rabbit antihuman gastrin I (E. R. Squibb & Co., NJ) and peroxidase conjugated swine antirabbit gamma globulin (Accurate Chemical, Westbury, NY).[33] Five photomicrographs were taken per each specimen and were printed with a final magnification of 100 times. All gastrin cells were counted per 1 mm of actual longitudinal length of mucosa, by choosing gastrin cell-rich areas.

Radiologic and Surgical Differentiation

Localization of the tumor source of the hypergastrinemia may occasionally be attained by computerized tomography of the pancreas and liver in patients with ZES.[34] Additionally, radiologic angiography may be helpful,[35] particularly when combined with percutaneous transhepatic portal venography for serial selective venous assays for serum gastrin and pancreatic polypeptide.[36] Pancreatic gastrinomas as well as one case of antral G cell hyperfunction have been confirmed by such selective techniques.[37]

While a clinical search for all ectopic sites of gastrinomas is indicated, the principle diagnostic differentiation between Ps-ZES and ZES lies in the thorough surgical exploration of the pancreatic–duodenal–hepatic area.[17] Finally, the ultimate discrimination is confirmed by postoperative serum gastrin and gastric acid measurements. Normal SG concentrations and achlorhydria after complete excision of the gastrinoma(s) or the antral source substantiate either diagnosis as correct, if the treatment has been appropriate. In ZES, surgical excision of all resectable tumor and total gastrectomy has resulted in normal serum gastrin concentrations in ten of 16 patients[17] and, to date, two patients with Ps-ZES (AGCH) have been reported who demonstrate resolution of their antral hypergastrinemia to normal levels after antrectomy with vagotomy.[8,38]

The purpose of this report is to document the prospective detection of patients having the characteristics of pseudo-Zollinger-Ellison syndrome by means of physiologic provocative testing, immunochemical studies of the antrum and surgical confirmation of diagnosis. An attempt is made to integrate the clinical, physiologic and pathologic parameters of the syndrome in order to adopt appropriate surgical treatment.

Results

The clinical, physiologic, radiologic, pathologic and therapeutic features in nine patients diagnosed as the pseudo-Zollinger-Ellison syndrome are documented in Table 1. Eight of the nine patients, to date, have had definitive operations for Ps-ZES, and all eight have immediately demonstrated normal SG levels and gastric anacidity after antrectomy. The symptomatology and clinical picture in each patient was sufficiently compelling to warrant surgical exploration for the presence or absence of tumor; none being found on thorough dissection in all patients, or on pancreatic biopsy in five patients, antrectomies with vagotomies were performed. Two of the eight patients having antrectomy had had prior truncal vagotomy and pyloroplasty or gastrojejunostomy with recurrence of ulceration requiring cimetidine treatment, and with persistence of hypergastrinemia and hyperacidity in spite of evidence of "complete" vagotomy by insulin-hypoglycemic stimulation. One patient with all the features of Ps-ZES, after vagotomy and pyloroplasty, is on cimetidine therapy and awaiting antrectomy.* The distribution of all the basal SG levels in these patients before and after antrectomy are shown on Figure 4, in comparison with randomized basal SG levels from the metabolic laboratory in patients with DU and proven ZES. Although there is some overlap in basal preoperative concentrations in the three groups, all patients with Ps-ZES had basal levels under 750 pg/ml. The results of the provocative tests in the nine patients with Ps-ZES are illustrated in Figure 5 and are similar in comparison with the reported results by Straus and Yalow in their patients designated as NTHH.[4] Mucosal stimulation by a standard test meal produced a marked increase of SG concentrations with

* Patient H.S. has subsequently had an antrectomy which resulted in a decrease in serum gastrin concentration (116 pg/ml).

TABLE 1. *Clinical Data in Nine Patients with Pseudo-Zollinger-Ellison Syndrome (Ps-ZES)*

Patient	Age/ Sex	Admission Diagnosis	Prior Treatment	Symptoms	X-ray +/or Endoscopic Findings	HCL C—mEq/L O—mEq/hr	Serum Gastrin (Preop) Basal (Pg/ml)	STM (% Δ)	Secretin (% Δ)	Ca^{++} (% Δ)	hPP (pMol/l) B	R	G Cell (no./mm)	Operation	Postop Basal SG (Pg/ml)	HCL (mEq)
C.O.	31F	Recurrent D.U.	CTD V & P	N & V Dysphagia Diarrhea Wt loss 25 lb	DU 2 cm Esophageal Stricture	BAC = 76 MAC = 58 (Insulin)	510	↑177%	↑32%	—	15	81	121 ± 5.1	Antrectomy with G-D Esoph. Dilat. Pancr. Bx*	36	NFA
D.G.	24F	ZES	V & P G-J	Hematemesis Pain Vomiting Diarrhea Wt loss 40 lb	Stomal ulcer Pyloric ulcer Esophagitis ↑ Rugae	BAO = 10 MAO = 16.4 (Pg)	349	↑267%	↑35%	—	13	53	73 ± 5.2	Antrectomy with G-J	71	NFA
M.G.	38F	Ps-ZES	CTD	Hematemesis Pain N & V Wt loss 43 lb	DU GU ↑ Rugae	BAC = 70 MAC = 118 (Pg)	443 560	↑219% ↑223%	↑3% ↑30%	↑↓0% —	29	111	96 ± 4.7	Antrectomy & Vagotomy	154	—
R.M.	46M	Ps-ZES	CTD	Pain Diarrhea Wt loss 17 lb	DU ↑ Rugae ↑ Duod folds	BAO = 11 MAO = 59 (Pg)	332	↑211%	↑1%	—	39	127	57 ± 4.1	Antrectomy & G-J & Vagotomy Pancr. Bx*	73	NFA
R.T.	39M	ZES	Antacids	Pain N & V	DU, postbulbar ↑ Rugae ↑ Duod folds	BAC = 68 MAC = 126 BAO = 13 MAO = 41 (Hist)	558	↑510%	—	↑↓0%	—	—	↑↑† @ 200	Antrectomy & G-J + Vagotomy Pancr. Bx	67	NFA
N.H.	49F	Secretory Diarrhea Ps-ZES	CTD Steroids Cholestyramine	Watery Diarrhea Wt loss 13 lb	↑ Rugae Esophageal Stricture Angio normal (VIP normal)	BAC = 39 MAC = 88 (Pg)	271	↑249%	—	↓3%	24	396	101 ± 6.7	Antrectomy & G-D and Vagotomy Pancr. Bx	57	NFA
M.D.	44F	ZES	Fundoplication	Pain Nausea Diarrhea Wt loss 40 lb	Esoph. ulcer DU Angio ? CT-pos.	BAO = 15.7 MAO = 15.8 (Pg)	295	↑169%	↓18% ↑↓0%	↑5%	20	220	95 ± 5.1 89 ± 4.3	Antrectomy & G-D and Vagotomy Exc. access. spleen Pancr. Bx*	89	NFA
B.P.	51F	ZES	CTD Antacids	Pain N & V Melena Diarrhea	DU, postbulbar GU Hiatal hernia Sono normal	BAO = 9.6 MAO = 9.3 (Pg)	190	↑215%	↑23%	—	43	172	85 ± 3.1	Antrectomy & G-D and Vagotomy	126	NFA
H.S.	66M	Recurrent DU	V & P CTD	Hematemesia Melana	Bleeding DU Histal hernia	BAO = 13.4 MAO = 14.0 (Pg)	212	↑260%	↑1%	↑10%	49	198	—	Awaiting Operation	—	—

Abbreviations: HCL = Gastric acidity; BAC = Basal acid concentration in mEq/liter; MAC = Maximal acid concentration; BAO = Basal acid output in mEq/hour; MAO = Maximal acid output; (Pg) = Pentagastrin stimulation; (Hist) = Histalog stimulation; NFA = No free acid; Pg/ml = Picograms per milliliter; STM = Standard Test Meal; Ca^{++} = Calcium stimulation; hPP = human Pancreatic Polypeptide; pmol/l = Picomoles per liter; B = Basal; R = Response to STM; G cell = Gastrin cell; DU = Duodenal ulcer; GU = Gastric ulcer; ZES = Zollinger-Ellison Syndrome; Ps-ZES = Pseudo-Zollinger-Ellison Syndrome; N & V = Nausea and vomiting; Pancr. Bx = Pancreatic biopsy; G-D = Gastroduodenostomy; G-J = Gastrojejunostomy; V & P = Vagotomy and pyloroplasty; CTD = cimetidine; VIP = Vasoactive intestinal polypeptide.

* Small focal areas of islet cell hyperplasia were noted in patients C.O. and R.M.; nesideoblastosis was observed in M.D.

† G cell stain with Toluidine Blue demonstrated approximately an eight-fold increase over normal in cross-section G cell population and the tissue content antral mucosal gastrin was 2,872 pg/mg.

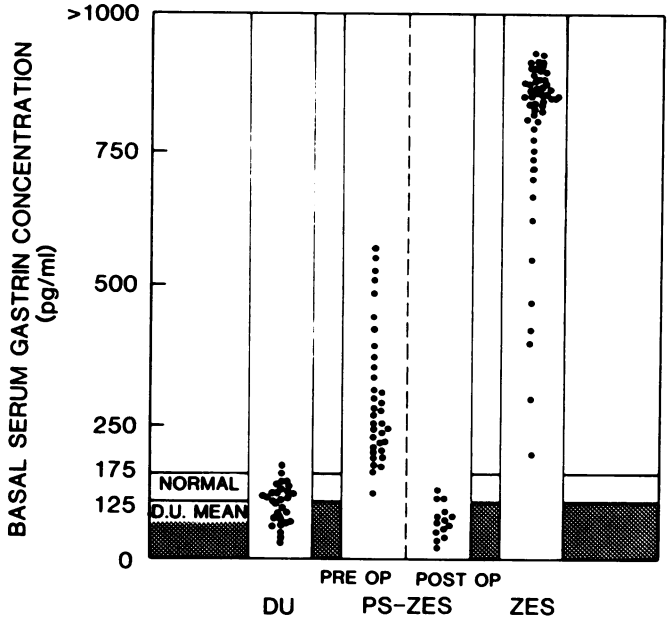

FIG. 4. Graph of basal fasting serum gastrin concentrations in nine patients with Ps-ZES, preoperatively and postoperatively, compared with random preoperative sampling in other patients with proven duodenal ulcer disease and the Zollinger-Ellison Syndrome.

an average increase of 250% over basal levels in the nine patients. Secretin stimulation caused no significant change (an average increase of 12%) and calcium stimulation similarly resulted in a mean increase of 2%. The overall diagnostic, provocative and therapeutic effects on serum gastrin concentrations are shown in Figure 6. Serum gastrin levels remained static or increased in the patients receiving cimetidine therapy. The symptoms in the five patients receiving cimetidine were temporarily improved; in the eight patients having antrectomy, the ulcers and symptoms were resolved.

The preoperative basal plasma hPP concentrations and the hPP response to the STM are shown in Table 1. There was no elevation of the basal hPP levels in the eight patients tested, which conforms with the absence of pancreatic gastrinomas; the hPP response to a STM was exaggerated in three patients, consistent with either AGCH or focal islet hyperplasia.

There was one false-positive angiograph and CT scan in patient M.D., which proved at operation to be an accessory spleen.

The antral G cell counts in the eight patients with Ps-ZES who underwent operation and in other patients with and without ulceration are illustrated in Figure 7. There was some overlapping of values between the groups, but the G cell population as determined in this investigation was highest in the Ps-ZES patients (range of 57 to 121 G cells per mm length of mucosa, an average of 102 G cells-mm). These values contrast to the average G cell count of 45/mm in "normal" patients without ulceration, 56/mm in DU patients, and 51/mm in patients with pancreatic gastrinomas (ZES). An average G cell count of 91/mm was found in patients with AGCH associated with other apudomas, hyperparathyroidism and MEA,I, with and without ulceration, as has previously been qualitatively observed.[3,30] Comparative photomicrographs of immunoperoxidase staining of antral mucosa are illustrated in Figure 8.

Discussion

It is apparent from these studies that the antrum and its surgical excision, even after vagotomy with drainage procedures, is important in the pathogenesis

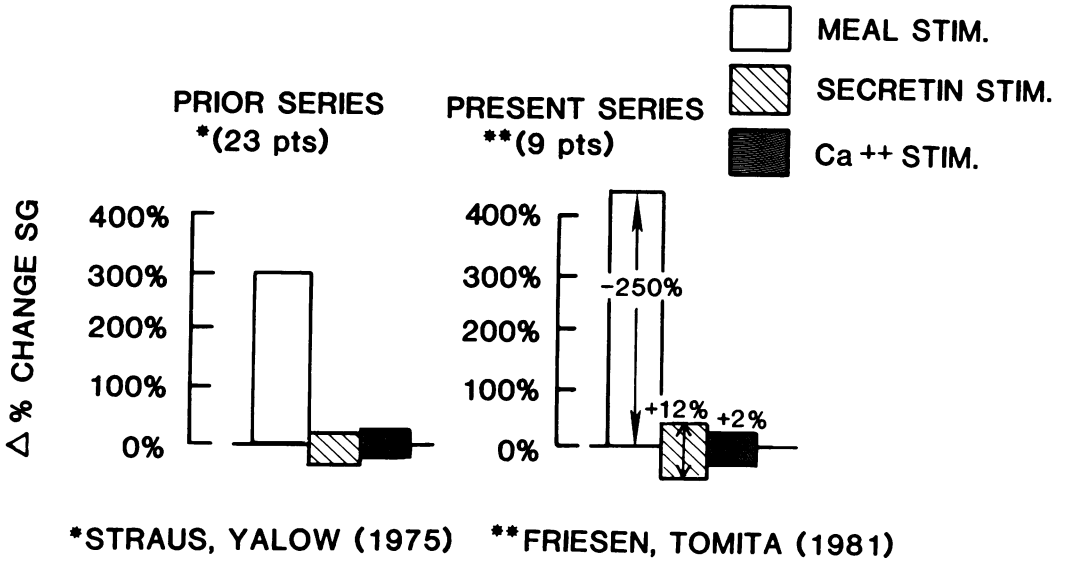

FIG. 5. Results of provocative testing in nine preoperative patients having Ps-ZES on the right, compared with similar results in a series reported by Straus and Yalow in 1975. (4) The mucosal (antral) source of the hypergastrinemia is characterized by an exaggerated response to a standard test meal with an absence of either a significant decrease or increase in serum gastrin concentrations on stimulation by a "secretin push" or calcium infusion.

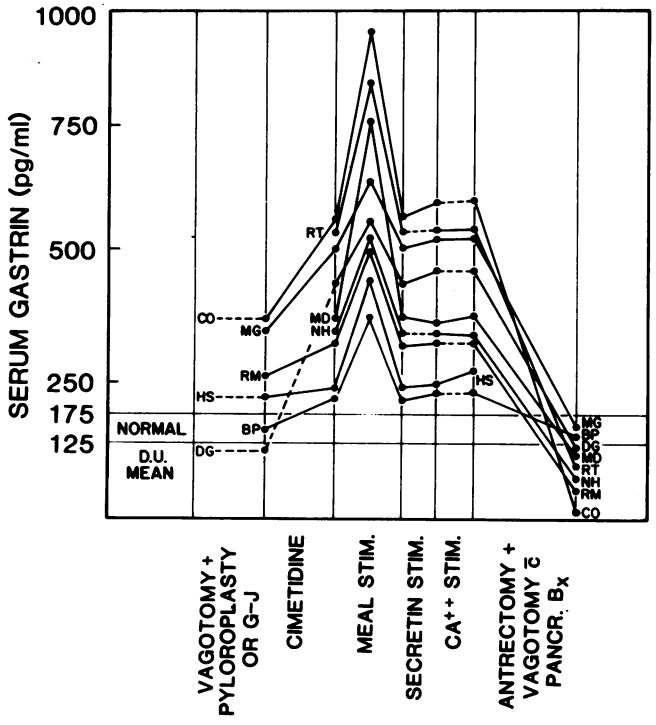

FIG. 6. Serum gastrin responses to provocative testing in nine patients and surgical antrectomy in eight patients characterized as having the Pseudo-Zollinger-Ellison Syndrome. One patient (H.S.) has not had surgical treatment as yet.

and treatment of Ps-ZES patients in whom ZES was strongly considered as the initial diagnosis. The symptoms in these patients were undoubtedly related to the gastric hyperacidity, relieved either palliatively by cimetidine, or curatively by elimination of the source of hypergastrinemia with antrectomy. The hyperacidity did not suppress or inhibit antral gastrin release as it does in neurogenic DU or normal subjects; thus the moderate hypergastrinemia could be considered to be "inappropriately" elevated for the degree of hyperacidity present. However, these studies support the concept that the "inappropriate" hypergastrinemia is not owing to the failure of acid inhibition but, rather, is due either to physiologically hyperactive antral G cells or more likely to pathologically hyperplastic G cells that excessively secrete gastrin. The peak serum gastrin response to food stimulation and the failure of a "secretin push" to elevate SG support a mucosal pathogenesis; the highest G cell counts in AGCH are indicative of a primary pathologic abnormality rather than merely a physiologic inappropriateness. That the gastric hyperacidity was not primarily vagally mediated or of neurogenic origin is suggested in the patients in whom acid hypersecretion persisted after vagotomy and resolved after antrectomy. In this study no basal SG concentrations prior to vagotomy with drainage were available; therefore it is not known whether the hypergastrinemia developed before or after vagotomy with drainage. It is doubtful and only speculative that the AGCH may have been initiated at the time of vagotomy. Since AGCH with and without hypergastrinemia has also been observed to occur in the detection of the MEA,I trait in families, it may or may not follow that the AGCH in Ps-ZES is genetic in origin, rather than secondary to an environmental hyperacidity state. None in this series of patients with Ps-ZES demonstrated a second APUD abnormality, but one patient (C.O.) gave a strong positive family history of duodenal ulcer on her paternal side. This patient may represent a subgroup of patients who have been reported to have familial duodenal ulcer disease with antral G cell hyperfunction, physiologically, and hyperpepsinogenemia.[45] Hypergastrinemia and/or AGCH have also been observed in association with other endocrinopathies[3,30,39,40] and in various other conditions sometimes associated with ulceration, such as in postoperative patients with retained, excluded

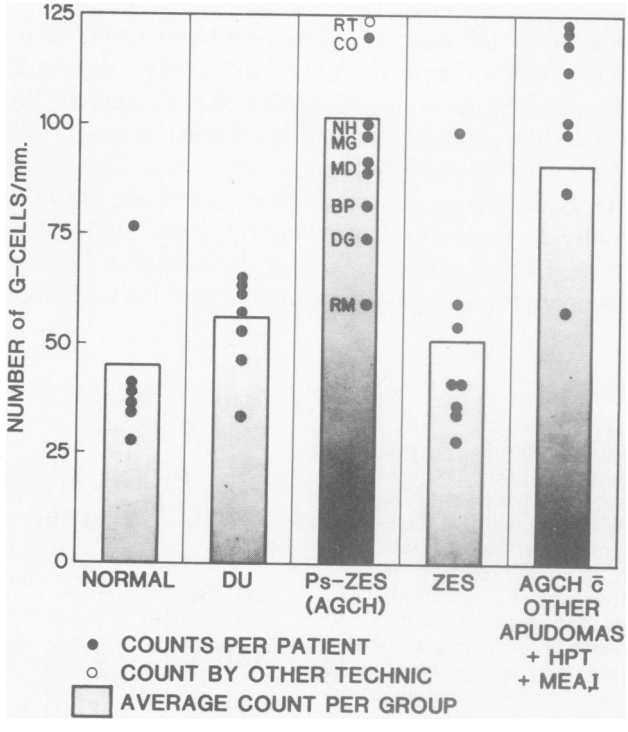

FIG. 7. Graph illustrating actual antral gastrin cell counts per longitudinal section of 1 mm antral mucosa in eight operated patients having AGCH in Ps-ZES and in randomly selected patients diagnosed as "normal", duodenal ulcer, ZES, and a group having AGCH associated with other apudomas, hyperparathyroidism and MEA, Type I.

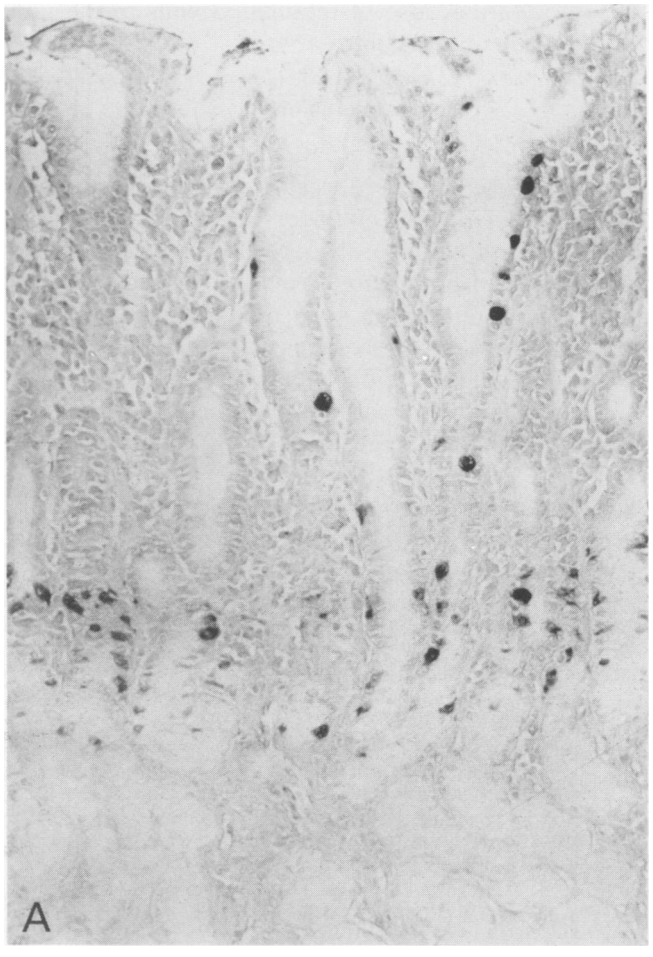

FIG. 8A. Photomicrograph illustrating immunoperoxidase staining of antral gastrin cells in pure antral G cell hyperplasia in Ps-ZES in patient (N.H.). There are numerous gastrin cells predominantly in the middle third of the mucosa. Scattered gastrin cells extend into the upper third of the mucosa. Gastrin cells have plump cytoplasms, strongly positive for gastrin.

antrum[41] or after small intestinal resections (short bowel syndrome),[42] and in patients with reduced catabolism of gastrin.[43]

While most of the above hypergastrinemic states can be easily diagnosed clinically, the practical problem facing surgeons consists of the differentiation between severe ulcerogenic states of DU, Ps-ZES and ZES, which require the benefit of provocative testing. In addition to the basal SG concentrations and the response to food, the intravenous secretin stimulation test is most practical and clearly discriminates between the three states. The physiologic mechanisms involved in secretin stimulation are not known; for some reason the normal ability of exogenous secretin to depress serum gastrin levels is lost in patients with an abnormal source of gastrin release from either the antrum in Ps-ZES or from tumor in ZES. This repeatable observation further suggests that the AGCH in Ps-ZES is an autonomous entity and thus pathogenetically important.

Gastric analyses are not discriminatory and are often inaccurate, but an effort should be made to ascertain if acid hypersecretion is present in ulcer patients with moderate hypergastrinemia. A more accurate representation of acid secretory function will probably be possible with further development of assays for endogenous secretin, which also assist in the monitoring of the effectiveness of cimetidine therapy.[44]

The two patients in this series who had focal islet cell hyperplasia on pancreatic biopsies also demonstrated an increased plasma hPP response to meals; it is doubtful that the minimal islet cell hyperplasia is a cause of the hypergastrinemia in these patients, particularly in view of the fact that SG concentrations decreased to normal levels after antrectomy.

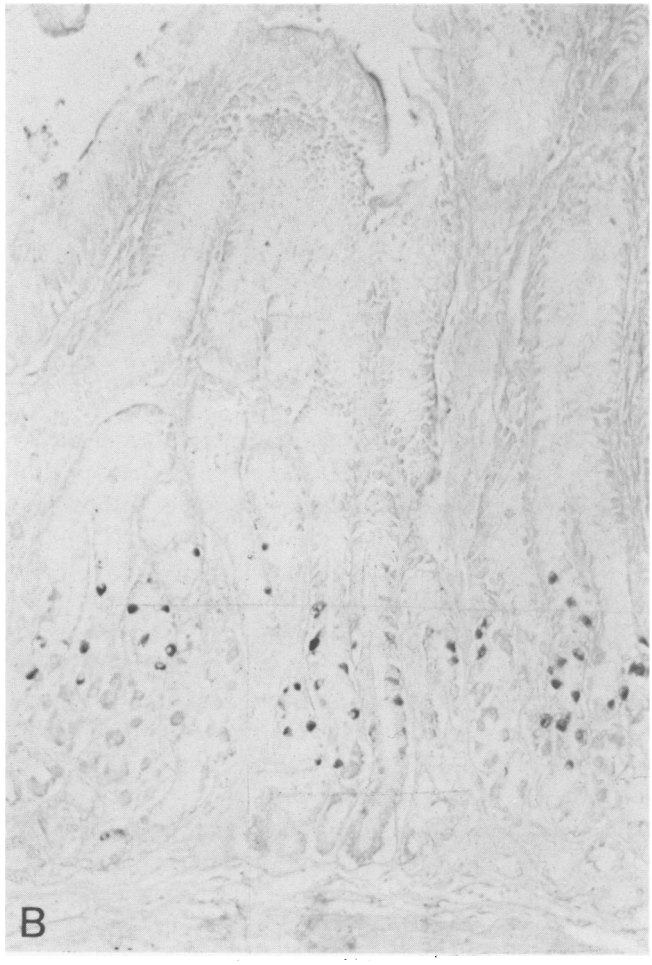

FIG. 8B. Normal control antral mucosa. Gastrin cells with relatively small cytoplasms are limited in the middle third of the mucosa.

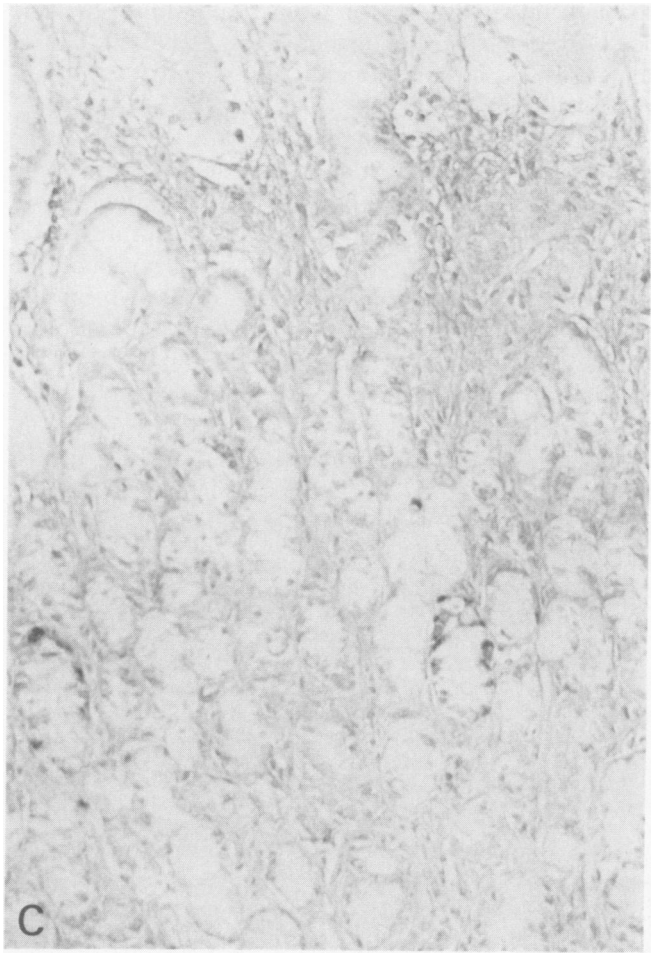

FIG. 8C. Decreased gastrin cells in a patient with duodenal ulcer. Fewer gastrin cells are observed in the middle third of the mucosa (Original magnification ×100).

The hyperplasia of the hyperfunctioning antral G cells in these initial studies is apparently the cause of the moderate hypergastrinemia observed in these patients. The preoperative endoscopic antral biopsy of small bits of mucosa may not always reflect the accurate cell counts obtained from surgically obtained specimens of antral mucosa. If the endoscopic biopsy does yield gastrin cell-rich areas, a preoperative confirmation can be obtained; however, multiple sections of antrectomy specimens were more representative of AGCH when compared with the endoscopy specimens in the same patients.

Two patients had repeat provocative testing by STM and secretin push postoperatively, at which time the characteristic features of Ps-ZES were not observed. Both had reconstruction after antrectomy by gastrojejunostomy. It has been reported that after reconstruction by gastroduodenostomy, stimulation by a STM may produce an elevation of serum gastrin concentration because of retained G cells in the first portion of the duodenum.[46]

Conclusions

Based on studies in nine patients who presented with clinical findings of severe, recurrent ulcer disease and diarrhea simulating the Zollinger-Ellison syndrome, the entity of an antral mucosal source for moderate hypergastrinemia without tumor may be designated as pseudo-Zollinger-Ellison syndrome. Stimulation by a meal and a lack of any response to a "secretin push" and calcium infusion differentiates this condition from the neurogenic duodenal ulcer diathesis and the pancreatic gastrinoma syndrome. Surgical antrectomy, even after vagotomy with drainage, results in clinical amelioration of ulcer symptoms and normal serum gastrin concentrations by the ablation of the hyperfunctioning hyperplastic gastrin cells of the antrum.

References

1. Zollinger RM, Ellison EH. Primary peptic ulceration of the jejunum associated with islet cell tumors of the pancreas. Ann Surg 1955; 142:709–728.
2. Friesen SR, Kimmel JR, Tomita T. Pancreatic polypeptide as screening marker for pancreatic polypeptide apudomas in multiple endocrinopathies. Am J Surg 1980; 139:61–72.
3. Friesen SR, Schimke RN, Pearse AGE. Genetic aspects of the Z-E syndrome: Prospective studies in two kindred: antral gastrin cell hyperplasia. Ann Surg 1972; 176:370–383.
4. Straus E, Yalow RS. Differential diagnosis of hypergastrinemia. *In* Thompson JC, (ed) Gastrointestinal Hormones. Austin, New Texas Press, 1975. pp. 99–113.
5. Polak JM, Stagg B, Pearse AGE. Two types of Zollinger-Ellison syndrome. Immunofluorescent, cytochemical and ultrastructural studies of the antral and pancreatic gastrin cells in different clinical states. Gut 1972; 13:501–512.
6. Cowley DJ, Dymock IW, Boyes BE, et al. Zollinger-Ellison syndrome type 1: clinical and pathological correlations in a case. Gut 1973; 14:25–29.
7. Pearse AGE, Bussolati G. Immunofluorescence studies of gastrin cell distribution in different clinical states. Gut 1970; 11:646–648.
8. Wilson RY, Boyes BE, Stagg BH, et al. Antral G-cell hyperplasia with hypergastrinaemia producing a Zollinger-Ellison syndrome. Gut 1972; 13:848–849.
9. Berson SA, Yalow RS. Radioimmunoassay in gastroenterology. Gastroenterology 1972; 62:1061–1084.
10. Friesen SR. The Zollinger-Ellison syndrome. *In*. Ravitch MM (ed) Current Problems in Surgery. Chicago, Year Book Medical Publishers, April, 1972; 1–52.
11. Ganguli PC, Polak JM, Pearse AGE, et al. Antral-gastrin-cell hyperplasia in peptic-ulcer disease. Lancet 1974; 583–586.
12. Keuppens F, Willems G, DeGraef J, Woussen-Colle MC. Antral gastrin cell hyperplasia in patients with peptic ulcer. Ann Surg 1980; 191:3:276–281.
13. Goligher JC, Feather DB, Hall R, et al. Several standard elective operations for duodenal ulcer: Ten to 16 year clinical results. Ann Surg 1979; 189:1:18–24.
14. McCarthy DM. The place of surgery in the Zollinger-Ellison syndrome. N Engl J Med 1980; 302:24:1344–1347.
15. Zollinger RM, Ellison EC, Fabri PF, et al. Primary peptic ulcerations of the jejunum associated with islet cell tumors: twenty-five year appraisal. Ann Surg 1980; 192:422–430.

16. Friesen SR, Hermreck AS, Brackett CE, Schimke RN. Cimetidine in the management of synchronous crises of MEA I. World J Surg 1980; 4:123–129.
17. Friesen SR. Treatment of the Zollinger-Ellison Syndrome—a twenty-five year assessment. Am J Surg 1981 in press.
18. Korman MG, Soveny C, Hansky J. Serum gastrin in duodenal ulcer. Gut 1971; 12:899–902.
19. Deveney CW, Deveney KS, Jaffe BM, et al. Use of calcium and secretin in the diagnosis of gastrinoma (Zollinger-Ellison syndrome). Ann Intern Med 1977; 87:680–686.
20. Bradley E, Galambos JT. Diagnosis of gastrinoma by the secretin suppression test. Surg Gynecol Obstet 1976; 143: 784–788.
21. Passaro E Jr, Basso N, Walsh JH. Calcium challenge in the Zollinger-Ellison syndrome. Surgery 1972; 72:60–67.
22. Polak JM, Adrian TE, Bryant MG, et al. Pancreatic polypeptide in insulinomas, gastrinomas, vipomas and glucagonomas. Lancet 1976; 1:328–330.
23. Lamers CBH, Diemel JM, Roeffen W. Letter to the editor. Lancet 1978; 2:326.
24. Kimmel JR, Hayden LJ, Pollock HG. Isolation and characterization of a new pancreatic polypeptide hormone. J Biol Chem 1975; 250:9369–9376.
25. Larsson LI, Ljungberg O, Sundler F, et al. Antro-pyloric gastrinoma associated with pancreatic nesidioblastosis and proliferation of islets. Virchows Arch (Pathol Anat) 1973; 360:305–314.
26. Bhagavan BS, Hofkin GA, Woel GM, Koss LG. Zollinger-Ellison Syndrome. Ultrastructural and histochemical observations in a child with endocrine tumorlets of gastric antrum. Arch Pathol 1974; 98:217–222.
27. Hardy JD. Personal communication, 1981.
28. Goodrick WIM, Dockery MD. Zollinger-Ellison syndrome associated gastric tumor showing islet-cell features. Minn Med 1963; 46:634–639.
29. Royston CMS, Brew DStJ, Garnham JR, Stagg BH, Polak J. The Zollinger-Ellison syndrome due to an infiltrating tumour of the stomach. Gut 1972; 638–642.
30. Friesen SR, McGuigan JE. Ectopic apudocarcinomas and associated endocrine hyperplasias of the foregut. Ann Surg 1975; 182:371–385.
31. Russo A, Buffa R, Grasso G, et al. Gastric gastrinoma and diffuse G cell hyperplasia associated with chronic atrophic gastritis. Endoscopic detection and removal. Digestion 1980; 20:416–419.
32. Polak JM, Bloom SR, Bishop AE, McCrossan MV. D cell pathology in duodenal ulcers and achlorhydria. Metabolism 1978; 27:9:1239–1242.
33. Taylor CR. Immunoperoxidase techniques. Arch Pathol Lab Med 1978; 102:113–121.
34. Dunnick NR, Doppman JL, Mills SR, McCarthy DM. Computed tomographic detection of nonbeta pancreatic islet cell tumors. Radiology 1980; 135:117–120.
35. Giacobazzi P, Passaro E Jr. Preoperative angiography in the Zollinger-Ellison syndrome. Am J Surg 1973; 126:74–76.
36. Ingemansson S, Larsson LI, Lunderquist A, Stadil F. Pancreatic vein catheterization with gastrin assay in normal patients and in patients with the Zollinger-Ellison syndrome. Am J Surg 1977; 134:558–563.
37. Thompson NW. Personal communication 1980.
38. Friesen SR. Current dimensions of the endocrine system. *In* Longmire WP Jr, (ed) Advances in Surgery. Chicago, Year Book Medical Publishers, 1976; 10:23–59.
39. Stremple JF, Watson CG. Serum calcium, serum gastrin, and gastric acid secretion before and after parathyroidectomy for hyperparathyroidism. Surgery 1974; 75:6:841–852.
40. Polak JM, Bussolati G, Pearse AGE. Cytochemical, immunofluorescence and ultrastructural investigations on the antral G cells in hyperparathyroidism. Virchows Arch Abt B Zellpath 1971; 9:187–197.
41. Korman MG, Scott DF, Hansky J, Wilson H. Hypergastrinaemia due to an excluded gastric antrum: A proposed method for differentiation from the Zollinger-Ellison syndrome. Aust NZ J Med 1972; 3:266–271.
42. Straus E, Gerson CD, Yalow RS. Hypersecretion of gastrin associated with the short bowel syndrome. Gastroenterology 1974; 66:175–180.
43. Korman MG, Laver MC, Hansky J. Hypergastrinemia in chronic renal failure. Br Med J 1972; 1:209–210.
44. Straus E, Greenstein RJ, Yalow RS. Plasma-secretin in management of cimetidine therapy for Zollinger-Ellison syndrome. Lancet 1978; 7:73–75.
45. Calam J, Taylor IL, Dockray GJ, et al. Subgroup of duodenal ulcer patients with familial G cell hyperfunction and hyperpepsinogenemia I. Gut 1979; 20:A934.
46. Grossman MI. Physiology and pathophysiology of gastrin. Clin Gastroenterol 1974; 3:533–538.

Discussion

PROFESSOR IVAN D. A. JOHNSTON (Newcastle upon Tyne, England): Andrew Kay in Glasgow first described a group of patients with duodenal ulcer who had recurrence after complete truncal vagotomy and whose gastric acid secretion was unaffected by the complete vagotomy. These patients required an antrectomy to reduce their acid secretion and heal their ulcers.

The demonstration of G-cell hyperplasia in the antrum of some patients with duodenal ulcers by immunofluorescent techniques was the next step in our understanding of this condition.

Interest in identifying these patients flagged mainly because the results of peptic ulcer operations were satisfactory. It did not, therefore, seem important, particularly when antrectomy was being added to vagotomy as routine in many centers, to try and identify this group of patients.

There are, however, several reasons for identifying those peptic ulcer patients who have this syndrome.

It is important to diagnose gastrinomas as early as possible in their development.

The introduction of H_2 blockade for the treatment of duodenal ulcer has reduced the number of gastric operations. Vagotomy alone is the operation chosen for many patients who have failed to respond to cimetidine or who have relapsed after a long course of H_2 blockers.

There is some evidence that the recurrence rate after vagotomy in these patients is high. The patients Dr. Friesen describes will be more numerous in the population of cimetidine failures coming to operation. Screening studies should produce a higher yield and allow the appropriate surgical treatment to be planned. The screening procedure must be simple, inexpensive and accurate.

Gastrin can be identified in gastric secretions. Was luminal gastrin measured, and is its measurement of value in identifying these patients? Does Dr. Friesen think that the increase in the levels of plasma gastrin following cimetidine treatment is of diagnostic importance because the gastrin level in patients with gastrinoma does not alter after cimetidine is given.

Should we be measuring serum gastrin, before and three hours after a standard meal as well as carrying out a secretin test, or can we omit the secretin test?

The objective in gastric surgery is to be both physiologic and offer the operation most suited to the patient's requirements. This