

Prospective Study of Gastrinoma Localization and Resection in Patients with Zollinger-Ellison Syndrome

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In 1982, a prospective study was initiated of 52 consecutive patients with proven Zollinger-Ellison syndrome (ZES), involving surgical exploration with the goal of removing the gastrinoma after an extensive protocol to localize the tumor. Each patient underwent ultrasound, computed tomography (CT) with oral/intravenous (IV) contrast, and selective arteriography. Eighteen patients had metastatic disease identified by imaging studies and confirmed by percutaneous biopsies, and two patients had multiple endocrine neoplasia type I (MEN-I) with negative imaging studies; therefore, these 20 patients did not undergo laparotomy. Each of the remaining 32 patients (3 with MEN-I and positive imaging studies) underwent laparotomy, and gastrinomas were removed in 20 patients. Preoperative ultrasound localized tumors in 20% of patients, CT in 40%, arteriography in 60%, and any of the modalities in 70% of patients. Infusion CT and arteriography were 100% specific. In 18 patients with either negative imaging (17) or false-positive imaging (1 ultrasound), gastrinomas were found and removed in six patients (33%). Twenty-four gastrinomas were found in 20 patients at laparotomy: eight in lymph nodes around the pancreatic head, four in the pancreatic head, one in the pancreatic body, three in the pancreatic tail, three in the pyloric channel, one in the duodenal wall, two in the jejunum at the ligament of Treitz, one in the ovary, and multiple liver metastases in one patient. If one excludes patients with MEN-I or liver metastatic disease, 12/28 (43%) of patients were biochemically "cured" immediately after operation. This result decreased to 7/23 (30%) with greater than 6 months follow-up. No patients with gastrinomas resected have developed recurrent gastrinoma on follow-up imaging studies (longest follow-up: 4 years). This study indicates that 95% of metastatic gastrinoma can be diagnosed before operation and that, by a combination of careful imaging studies and thorough exploration at surgery, 30% of patients with gastrinomas may be curable.

IN 1954, ZOLLINGER AND ELLISON first described a syndrome associated with severe peptic ulcer diathesis and pancreatic tumors.¹ The syndrome would later bear their name, and their initial treatment, total

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gastrectomy, is still believed by some to be the treatment of choice.² However, the ability to control the acid hypersecretion medically initially with cimetidine³ and now with more potent H₂ antagonists⁴ and drugs with different mechanisms like omeprazole⁵ has in our experience eliminated the need for total gastrectomy or any other operation to reduce acid output.⁵

With improved ability to diagnose Zollinger-Ellison syndrome (ZES) and widespread effective means to control gastric acid hypersecretion either by drug management^{4,5} or total gastrectomy,² it is apparent that the natural history of the malignant gastrinoma has become the most important determinant of long-term survival of patients with ZES. It is believed that 90% of gastrinomas are malignant,⁶ and Zollinger has shown that patients with metastatic disease have a 5-year survival rate of 42%.⁷ In addition, preliminary reports suggested that surgical removal of the gastrinoma was possible in a greater number of patients than previously reported^{8,9} and that newer preoperative localization studies such as transhepatic sampling of the portal venous tributaries for gastrin might further assist in localization.^{10,11} Based on these observations, in 1982 we instituted a prospective study of the ability to localize and resect gastrinomas for cure of patients with ZES. We reported our initial results on the first seven patients in this study previously.¹² We now present data on 52 consecutive patients with ZES who underwent localization studies, of whom 32 subsequently underwent laparotomy, while 20 patients were not subjected to laparotomy because of either metastatic disease or Multiple Endocrine Neoplasia-I (MEN-I) without gastrinoma detectable before operation (N = 2). This paper reports the largest series of patients with ZES in whom

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Materials and Methods

Fifty-two consecutive patients referred to the National Institutes of Health from 1982 to the present with a diagnosis of ZES were studied in a prospective manner according to an approved protocol. The diagnosis of ZES was initially confirmed in all patients by performing the following studies: measurement of fasting serum gastrin concentration by radioimmunoassay (Bioscience Laboratories, New York, NY, using Walsh gastrin antibody No. 1611 (lot 4A), which recognizes gastrin-17 and gastrin-34 equally), secretin and calcium provocative testing performed as outlined previously,¹³⁻¹⁵ and basal and pentagastrin stimulated maximal acid output in the absence of antisecretory medication, as described previously.^{3,16}

ZES was established biochemically by the following criteria: fasting serum gastrin concentration greater than 100 pg/ml; basal acid output greater than or equal to 15 mEq/h if the patient had had no previous gastric surgery, or greater than 5 mEq/h if the patient had had prior gastric surgery. An abnormal secretin test was defined as an increase in serum gastrin concentration of greater than 200 pg/ml following the intravenous (IV) administration of 2 U/kg of GIH secretin.¹³ Abnormal calcium infusion test was defined as an increase in serum gastrin concentration greater than 395 pg/ml following the infusion of 5 mg/kg elemental calcium per hour for 3 hours.¹⁴ All patients had at least two of four described criteria.

The antisecretory drug dosage requirement was that amount of antisecretory medication necessary to suppress gastric acid secretion to <10 mEq/h in the final hour prior to the next scheduled dosage determined as described previously.^{3,16} If the patient had prior gastric acid reduction surgery, then the amount of antisecretory medication to suppress acid output to <5 mEq/h was given. A dose of antisecretory medication to control gastric acid output as outlined above was achieved in all patients.

All patients (N = 52) underwent upper gastrointestinal (GI) series, upper GI tract endoscopy, computed tomography (CT) of the abdomen with and without intravenous contrast, abdominal ultrasonography, and selective hepatic, gastroduodenal, splenic, and superior mesenteric arteriography.^{4,17-19} All imaging studies were read prospectively by one radiologist (JLD). The results were available to the operating surgeon. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated²⁰ for the results of ultrasound, CT, selective arteriography, and all imaging studies combined. Histologically proven gastrinoma from exploratory laparotomy or percutaneous guided biopsy served as the

standard of reference. Patients with metastases that could be biopsied percutaneously or laparoscopically (N = 18) were excluded. Patients with multiple endocrine neoplasia type I (MEN-I) without tumor present on imaging studies (N = 2) were not explored. All remaining patients (N = 32) underwent percutaneous transhepatic venous sampling of the portal vein and its tributaries for gastrin prior to surgery. The method and results of portal venous sampling has been previously reported.²¹

All investigations were performed at the National Institutes of Health (NIH), and the first six patients underwent exploration at Walter Reed Army Medical Center by one surgeon (JWH). The remaining 26 patients underwent exploration at NIH by another surgeon (JAN). At laparotomy the liver, pelvis, small intestine, pancreas, stomach, duodenum, mesenteric, and retroperitoneal regions in the upper abdomen were carefully explored. The pancreas was examined visually and by careful palpation; the pancreatic head was inspected after an extended Kocher maneuver; the pancreatic body and tail were inspected by opening the lesser sac along the avascular plane of the transverse colon, and the inferior border of the pancreas was dissected free so the body and tail could be palpated between two fingers. The entire duodenum was carefully palpated, and any suspicious nodule in the wall was better exposed by opening the duodenum. The same extensive search was made regardless of the preoperative localization information or the operative findings. Any suspicious pancreatic, stomach, duodenal, bowel, or peripancreatic nodule or lymph node was removed for pathologic examination. In the bowel or stomach wall, a suspected tumor was excised with a full thickness rim of normal gut around the tumor. In the pancreatic head or adjacent lymph node areas, suspected tumors were enucleated. In the pancreatic tail, the distal pancreas and spleen were resected, except in one patient with MEN-I in whom the tumor was enucleated. In the one ovarian cyst adenocarcinoma that was producing gastrin, a total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed. If a gastrinoma was not located, no gastric resection was performed.

After surgery, all patients underwent fasting gastrin determination and secretin-provocative testing prior to discharge and were discharged on their preoperative antisecretory medication. Patients were re-evaluated at 3 months after operation and then yearly. If a gastrinoma was removed, a complete re-evaluation was performed at each follow-up visit, including biochemical testing and imaging (ultrasound, CT, arteriogram). Our criteria for "cure" of ZES include: (1) normal fasting serum gastrin (<100 pg/ml), (2) less than 200 pg/ml rise in serum gastrin following the administration of secretin, and (3) no evidence of tumor on follow-up imaging studies.

TABLE 1. Characteristics of 32 Patients with ZES Who Were Explored for Gastrinoma

Patient Number	Age (Years)/ Sex	Symptoms			Number of Previous Gastric Operations
		PUD	Diarrhea	MEN-I	
1	51/M	+	+	N	0
2	59/M	+	+	Y	0
3	36/M	+	+	N	0
4	46/F	-	+	N	0
5	35/M	+	+	N	0
6	31/F	+	+	N	0
7	56/F	+	-	N	0
8	44/M	+	+	N	1
9	38/M	+	+	N	0
10	66/M	-	-	N	1
11	47/F	-	+	N	0
12	63/M	+	+	N	1
13	55/M	+	+	N	0
14	23/M	+	+	Y	0
15	55/M	+	-	N	0
16	49/M	+	+	N	0
17	40/M	-	+	N	0
18	42/M	+	-	N	0
19	58/M	+	+	N	0
20	50/F	+	+	N	2
21	38/M	+	-	N	1
22	54/F	+	+	N	0
23	35/M	+	-	N	0
24	57/M	+	+	N	1
25	54/F	-	+	N	0
26	29/F	+	+	N	0
27	49/M	+	+	N	1
28	59/M	+	+	N	2
29	62/M	+	+	Y	2
30	36/M	+	+	N	0
31	61/M	+	+	N	1
32	53/F	+	+	N	0

PUD = peptic ulcer disease; MEN-I = multiple endocrine neoplasia type I; N = no; Y = yes.

As outlined in methods, all patients were initially considered for surgery, but patients with metastatic disease on imaging or MEN-I without localized tumor on imaging did not undergo laparotomy and their characteristics are not included in the table (N = 20).

Results

Clinical Characteristics

The clinical characteristics of the 32 patients who underwent exploratory laparotomy for ZES are listed in Table 1. Men predominated, being 72% of the total. The mean age was 48 years with a range between 23 and 66 years. Nearly all the patients (84%) had symptoms of peptic ulcer disease and indigestion, or diarrhea, or both. Patients with MEN-I were prospectively excluded unless they had positive imaging studies; thus, only three patients (9%) had MEN-I. Thirty-one per cent had prior gastric procedures, and three patients had had two prior procedures. The clinical characteristics of the 18 patients with demonstrable metastatic disease and the two MEN-I patients without demonstrable disease who were not explored were similar to those of the operated patients listed in Table 1.

Biochemical Diagnosis

The data necessary to establish biochemically the unequivocal diagnosis of ZES in the 32 operated patients are listed in Table 2. All 32 patients had an elevated basal acid output and an elevated fasting serum gastrin level. All but four patients had a basal acid output/maximum acid output greater than 0.6. All but one patient had an increase in serum gastrin level greater than 200 pg/ml following the intravenous administration of secretin, and that patient had a marked elevation in basal serum gastrin concentration and acid output consistent with ZES. Provocative testing with calcium was the least reliable test to discriminate ZES because ten patients did not increase their basal gastrin level greater than 395 pg/ml following the infusion of calcium. These studies, namely the elevated gastrin level and basal acid output (as well as the abnormal secretin test in 31 patients), biochemically established the diagnosis of ZES in all 32 operated patients. The 20 patients who were not explored all had values similar to those of the operated patients (data not shown).

Localization Tests

The results of all preoperative localization tests are given in Table 3 and Figure 1. Of the 20 patients with gastrinomas found, ultrasound was positive in 20%, CT in 40%, angiography in 60%, and any of the modalities in 70% (Fig. 1). Of the three imaging studies, only ultrasound gave a false-positive result (Fig. 1). Ultrasound was the least sensitive, infusion CT intermediate, and selective arteriography was the most sensitive single test at imaging tumors that were found at laparotomy. However, the combination of all three studies was more sensitive than any one study alone (Table 3, Fig. 1). In general, all imaging studies were very specific, especially CT and arteriogram, which were 100% specific (Table 3). Ultrasound was the least specific but was still 92%. The positive predictive value for all imaging studies was very good (80% for ultrasound and 100% for the other two); this means that, if a single study imaged the tumor, there was a high likelihood that the imaged tumor would be found. However, all of the localization tests had a fair-negative predictive value, meaning that even when all of the imaging studies were negative, a gastrinoma was found at exploration 33% of the time (Table 3).

Table 4 examines the ability of imaging studies to determine before operation the location and extent of gastrinoma in all 52 patients who presented with ZES. In 18 patients, the preoperative imaging detected liver metastases, and percutaneous biopsies confirmed the presence of liver metastases in all 18. Only one of 32 patients was found to have liver metastases at exploratory laparotomy when the preoperative imaging predicted that no liver metastases would be found. Therefore, preoperative im-

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TABLE 2. Biochemical Diagnosis of ZES in 32 Patients Prior to Exploratory Laparotomy

Patient Number	BAO (mEq/h)	BAO/MAO	Basal Gastrin (pg/ml)	Δ Secretin (pg/ml)	Δ Calcium (pg/ml)
1	48	0.92	3999	5002	9380
2	53	0.88	822	2660	4772
3	75	0.82	613	512	835
4	61	0.94	1994	530	4603
5	47	0.67	331	281	134
6	30	0.90	1131	4010	2005
7	28	0.64	325	1670	4470
8	159	1.0	756	2300	0
9	24	0.57	487	1435	3995
10	10	0.53	5650	9300	8675
11	62	0.98	7000	20100	22300
12	56	1.0	917	1396	394
13	28	0.35	211	211	208
14	44	0.57	748	570	1800
15	26	0.61	324	400	446
16	55	0.63	390	210	334
17	49	0.83	373	413	390
18	40	0.61	113	245	299
19	53	0.94	395	1509	1646
20	82	1.00	1139	830	1420
21	32	0.62	459	341	285
22	76	1.00	5057	2365	2150
23	36	0.92	460	512	N.D.
24	36	0.76	1197	820	713
25	37	1.00	864	744	400
26	42	0.52	436	5204	1542
27	42	0.61	195	457	735
28	83	0.80	360	400	404
29	23	0.96	2000	2480	480
30	66	0.68	641	129	203
31	8	0.73	618	1559	2297
32	25	0.80	268	686	119
$\bar{x} \pm$ SEM	48 ± 5	0.77 ± .03	1258 ± 302	2165 ± 673	2498 ± 787
Normal levels	<15 mEq/h (no prior gastric surgery)	<0.6	<100	<200	<395
	<5 mEq/h (prior gastric surgery)				

BAO = basal acid output; MAO = maximal acid output; basal gastrin = fasting gastrin concentration; Δ secretin = increase in serum gastrin concentration over basal after intravenous secretin (2 U/kg); Δ calcium = increase in serum calcium over basal after intravenous calcium infusion as outlined in methods.

As outlined in methods, all patients were initially considered for surgery, but patients with metastatic disease on imaging or MEN-I without localized tumor on imaging did not undergo laparotomy. Their biochemical results are similar to those of the operated group, but the data for the unoperated group (N = 20) are not shown in the table.

One patient (#22, Table 5) was identified to have liver metastases that were too numerous to count; that patient also had a primary tumor in the pancreatic head. The

TABLE 3. Results of Localization Studies in 32 Patients with ZES Who Underwent Laparotomy

	Ultrasound (%)	Infusion CT (%)	Selective Arteriography (%)	All Imaging (%)
Sensitivity	21	40	60	70
Specificity	92	100	100	92
Positive predictive value	80	100	100	93
Negative predictive value	44	50	60	67

All numbers shown are percentages. Sensitivity, specificity, and positive and negative predictive value are calculated as outlined in methods.

imaging studies correctly localized 18/19 patients with liver metastases. In the 20 patients with gastrinomas found at exploration, 14 had positive preoperative imaging and all 14 were located as radiographically predicted. However, 17 patients had completely negative preoperative imaging studies, and one patient (#26, Table 5) had a false-positive preoperative ultrasound; thus, 18 patients had incorrect imaging before operation, and tumor was found in six. Two patients with MEN-I and negative imaging were not explored. Therefore, considering that all 52 patients had ZES on admission, imaging studies correctly imaged 32/52 (62%) before operation, and exploratory laparotomy added six additional patients. Therefore, gastrinoma was proved histologically in 38/52 (73%) patients.

Tumor Location

Figure 2 diagrams the exact location of 24 gastrinomas found in 20 of 32 patients who underwent laparotomy.

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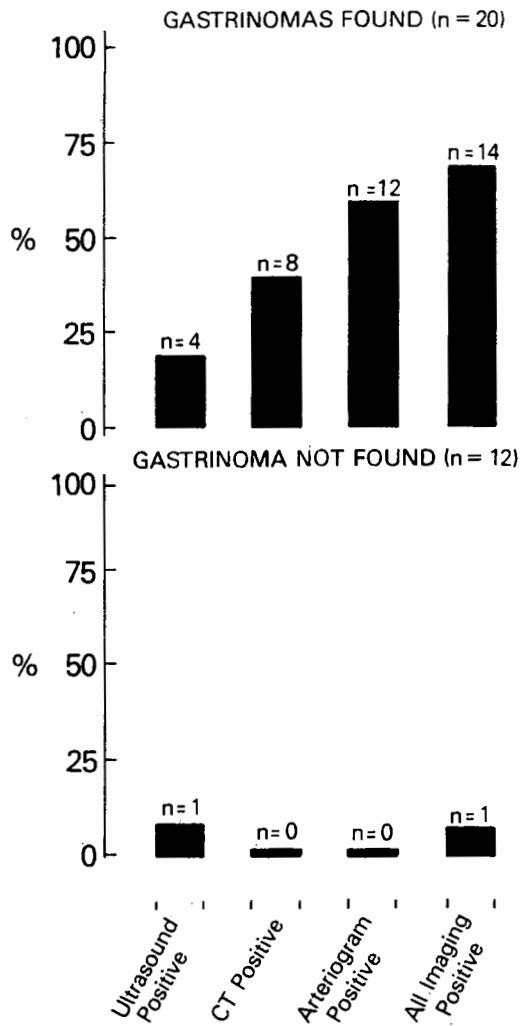


FIG. 1. Results of various imaging studies in patients with and without gastrinomas found. N refers to the number of patients with indicated surgical result who had a positive result on the indicated imaging test.

patient with liver metastases only had biopsy confirmation of the diagnosis; all other patients had all gross tumor resected, and three additional patients had more than one tumor. One patient with MEN-I had a pancreatic head primary and adjacent lymph node metastases (#29, Table 5), and two patients had two gastrinomas in lymph nodes around the pancreatic head without obvious primary tu-

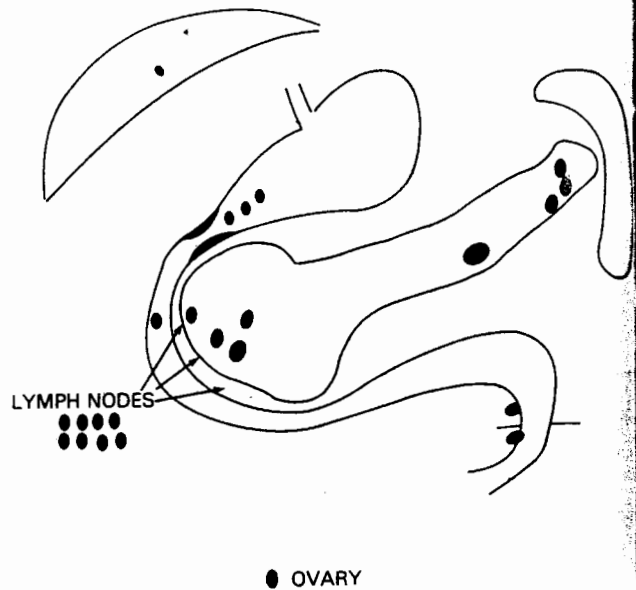


FIG. 2. Location of gastrinomas found. Twenty-four gastrinomas were found in 20 patients, and the location of each is indicated.

mors (#8 and 10, Table 5). Only one of four patients who had more than one gastrinoma (#10, Table 5) is biochemically "cured" with short follow-up.

Three tumors were found in the wall of the pyloric canal and one in the duodenal wall (#5, 17, 18, 21, Fig. 2, Table 5). These tumors were all less than 1 cm in largest dimension and were all excised with some normal full-thickness gut wall around the tumor. Follow-up of these patients indicates that only one patient is cured at 35 months (#5), while one patient has a normal gastrin but a positive secretin test at 19 months (#18).

Eight gastrinomas in seven patients were found in lymph nodes around the pancreatic head and duodenum (#2, 6, 8, 10, 11, 19, 29, Fig. 2, Table 5). This was the most common location for gastrinomas in this series. Four of seven patients were cured at 30, 6, 7, and 19 months.

Four patients were found to have pancreatic head tumors, and three of four had their gastrinomas enucleated (#1, 29, 30); two patients (#1, 30) are "cured" at 40 and 6 months' follow-up. One of the patients (#30) had a 6 cm tumor in the pancreatic head, which was easily enu-

TABLE 4. Ability to Localize and Determine before Operation the Extent of Gastrinoma in All Patients with ZES

Total # Patients	Metastatic Gastrinoma On Imaging	No Metastases On Imaging	Positive Preoperative Imaging	Negative Preoperative Imaging	Total
52	18/18 (100%)	1/32* (3%)	14/14 (100%)	6/18 (33%)	38/52 (73%)

Numerator refers to the number of patients with proven tumor either evaluated at surgery (N = 32) or by image-directed percutaneous biopsy (N = 18), and denominator is the number of patients with the indicated

result of imaging studies.

* Two patients with MEN-I had negative imaging and did not undergo exploration or percutaneous biopsies.

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TABLE 5. Preoperative Imaging Studies and Operative Course in Patients with Gastrinomas Found at Laparotomy

Patient Number	Combined Imaging Localization	Tumor Location and Size	Operation Done	Follow-up
1	PH	0.7 cm PH	Excision	"Cure" at 40 mo
2	PH	2 cm PH (LN)	Excision	BD
5	NEG	0.5 cm tumor duodenal wall	Excision	"Cure" at 35 mo
6	PH	1 cm PH (LN)	Excision	"Cure" at 30 mo
8	PH	1.5 cm PH (LN)	Excision	BD
10	PB	3 cm Ligament of Treitz 1 cm PH (LN)	Excision	"Cure" at 6 mo
11	PH	3 cm PH (LN)	Excision	"Cure" at 7 mo
14	PT	PT 2 cm	Excision	BD
17	NEG	0.6 cm pyloric canal	Excision	BD
18	NEG	0.4 cm pyloric canal	Excision	+ secretin; normal gastrin at 19 mo
19	PH	1 cm tumor PH duodenal wall (LN)	Excision	"Cure" at 19 mo
21	PH	0.6 cm tumor pyloric canal	Excision	BD
22	PH	Liver mets 5 cm tumor PH	Biopsy	Progressive liver mets
23	NEG	0.5 cm tumor jejunum wall Ligament of Treitz	Excision	Negative secretin; abnormal basal gastrin at 3 mo
25	OVARY	R ovarian cancer (gastrinoma)	TAH BSO	"Cure" at 3 mo
26	PB*	1.5 cm tumor PT	Distal pancreas	Normal gastrin; positive secretin 6 mo
29	PH	1.5 cm tumor PH 0.5 cm PH (LN)	Excision	BD
30	PH	6 cm tumor PH	Excision	"Cure" at 6 mo
31	PT	2.5 cm tumor PT	Distal pancreas	"Cure" after operation
32	NEG	2.5 cm tumor PT	Distal pancreas	"Cure" after operation

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This table includes only patients in whom gastrinomas were found at laparotomy. Twelve patients with biochemical evidence for ZES underwent laparotomy but no tumors were found. Their biochemical parameters did not change following laparotomy.

PH = pancreatic head; PB = pancreatic body; PT = pancreatic tail; LN = lymph node; Neg = negative; R = right; Mets = metastases; BD = biochemical disease only (no tumor on imaging studies); Secre-

cleated, and that patient remains "cured" at 6 months. Two patients presented with tumors in the jejunal wall around the ligament of Treitz (#10, 23); one was subsequently "cured" (#10), and one had slightly elevated basal gastrin level but negative secretin test (#23).

Patients who were found to have distal pancreatic body or tail lesions had resections, except for one patient with MEN-I who had an enucleation (#14). The others (#26, 31, 32) all had large tumors 1.5-2.5 cm in greatest dimension and underwent distal pancreatectomy and splenectomy. All three appeared "cured" at initial postoperative testing, but one (#26) has developed a positive secretin test at 6 months' follow-up. The solitary patient with a large primary right ovarian gastrinoma (#25) underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy and appeared "cured" at 3 months' follow-up.

"Cure" Rate and Follow-Up

If one examines the ability to "cure" these patients, as defined in the methods, the results appear to change with length of follow-up. Of the 32 operated patients, tumors

tin = positive or negative refers to the results of postoperative secretin test as defined in methods. Normal or elevated fasting gastrin refers to whether after operation fasting gastrin concentrations were in the normal range (≤ 100 pg/ml). "Cure" is used as defined in methods, i.e., indicating normal fasting gastrin concentration and negative secretin test at the follow-up time indicated.

* This localization was a false-positive.

were found in 20 patients; and in 12 patients with identical biochemical ZES, no tumors were identified at laparotomy. Postoperative follow-up of these 12 patients without gastrinoma resections showed that basal gastrin levels, increment in gastrin concentration following secretin administration, and basal acid output all remained unchanged. However, no patient in whom laparotomy did not find tumor had subsequently developed detectable gastrinoma on sequential imaging studies, and the maximum follow-up was 4 years after operation. Of the 20 patients with tumors found at laparotomy, 14 patients subsequently had normal basal gastrin and/or normal secretin test results immediately after surgery (Fig. 3). Of these 14, 12 were believed to be "cured"; that is, they had normal basal gastrin and secretin tests and were without tumor on imaging studies. Patients 8 and 11 had initial abnormal secretin tests (Fig. 3). Interestingly, in one patient (#8), secretin test remained abnormal with subsequent follow-up, and, at 2 years after operation, his basal gastrin level became elevated (Fig. 3). In contrast, patient #11, who had both abnormal secretin test and elevated basal gastrin levels immediately after operation, subsequently developed normal levels (Fig. 3). Long-term fol-

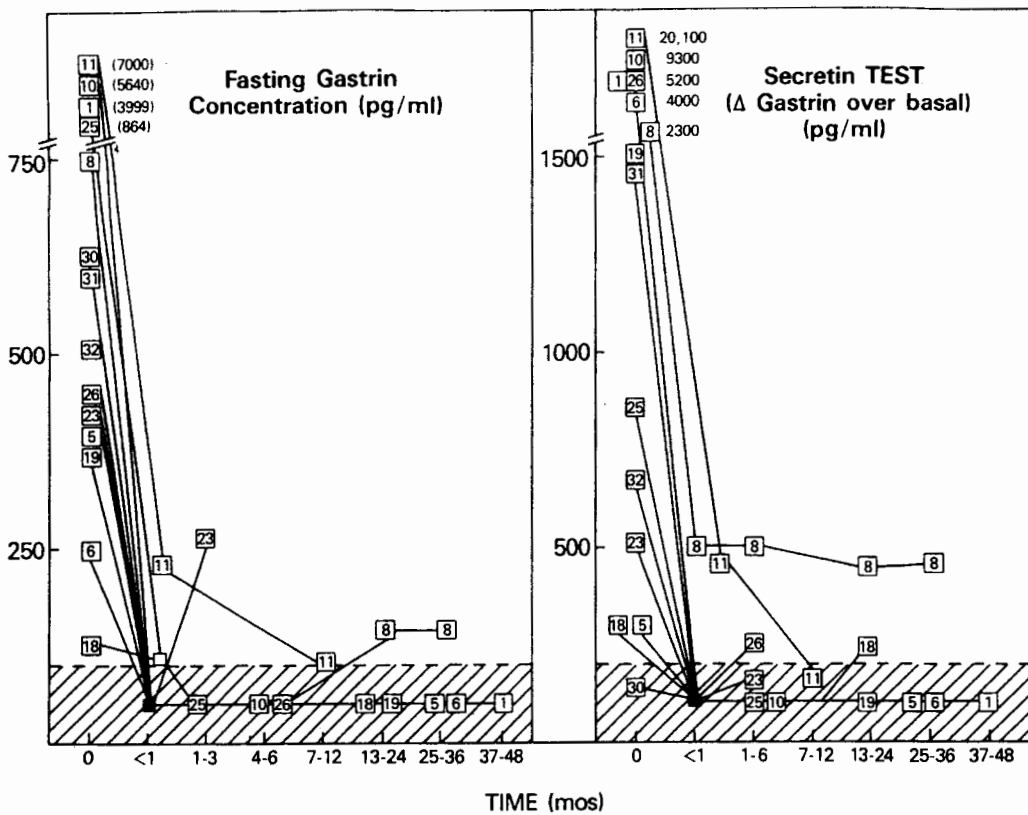


FIG. 3. Fasting serum gastrin concentrations and secretin test results before and after operation in all patients in whom gastrinomas were resected and basal gastrin and/or secretin test subsequently became normal. Number indicates patient number in Tables 1, 2, and 5. Time is in months after operation. Dotted line indicates the upper limit of the normal response, which is 100 pg/ml for fasting gastrin and less than 200 pg/ml for secretin test. Patients were evaluated before and immediately after operation (<1 mo), at 1-6 months, and then yearly, as indicated in methods.

low-up will be essential because two patients (#18 and 26) have developed abnormal secretin tests, but both still have normal basal gastrin levels and no detectable disease at 12 and 6 months, respectively. No patient who had tumor resected at laparotomy has subsequently developed recurrent gastrinoma detectable by imaging, including CT, ultrasound, and arteriogram.

In the operated patients, if we exclude the four patients with MEN-I or proven metastatic gastrinoma to the liver, the "cure" rate immediately after operation is 43%, and it appears to decrease with longer follow-up to 30% at a mean 2-year point (Table 6). Careful continued follow-

up will be necessary, as it appears that some patients will develop biochemically documentable recurrent disease with time (Fig. 3).

Discussion

The management of patients with ZES is evolving. The introduction of cimetidine,³ ranitidine,¹⁶ famotidine,²¹ and subsequently omeprazole⁵ has changed the role of surgery in the management of these patients.^{9,12,23} In the past, total gastrectomy was the procedure of choice to control the gastric acid output, but potent antisecretory

TABLE 6. "Cure" Rate

Patients Excluding MEN-I and Metastatic Liver Disease	Patients with Gastrinomas Found	Time Postoperative			No. Patients Who Subsequently Have Developed Tumor in Imaging Studies
		Immediate	3 Mo	>6 mo*	
28	17	12/28 (43%)	9/26 (35%)	7/23 (30%)	0

* \bar{X} = 20 mo.

"Cure" is used as defined in methods, i.e., indicating normal fasting gastrin concentration and negative secretin test at the follow-up time indicated. Exploratory laparotomy was done in 32 patients and the four

patients with either metastatic gastrinoma to the liver (N = 1, patient 13, Table 5) or MEN-I (N = 3, patients 2, 14, 29, Table 1) were excluded. MEN-I = multiple endocrine neoplasia type I; immediate = within 2 weeks after operation.

medications have Fifty-seven per cent of patients with ZES v 5-year survival of node metastases year survival of p is only 20%.²⁵

Given this clear tumor progression the potential role of minimal disease. The early diagnosis (MCT) in patients with ZES is of prognostic importance. The measurement of microscopic cancer is curable by total gastrectomy. In addition, the early diagnosis and leads to a distally curable, distal gastrectomy group. In addition, all but a few patients respond to secretin.

Potential difficulties in the follow-up for cure are described.²⁻⁹ The goal of any single local resection for ZES is to prevent possible mortality (procedure) or to cure patients who have possibly benign disease. Multiple in the pancreas tumor does not metastasize to distant sites. Interfering with the chemically "curable" liver gastrinoma finding any other in potential gas to find the gastrinoma. 34-40% of patients with gastrinoma found (73%) patients with proven histologically localized disease biochemically found, despite sampling, other exploration. Sc

medications have eliminated the need for this procedure. Fifty-seven per cent of patients with ZES who had a total gastrectomy subsequently died of tumor progression.^{6,24} Zollinger and Ellison have documented that 60% of patients with ZES will develop liver metastases and that the 5-year survival of patients with liver metastases and lymph node metastases is 42%. Our own results indicate that 5-year survival of patients with extensive metastatic disease is only 20%.²⁵

Given this clear potential for metastatic disease and tumor progression in patients with ZES, we considered the potential role of surgical exploration in patients with minimal disease and biochemical documentation of ZES. The early diagnosis of medullary thyroid carcinoma (MCT) in patients from kindreds with MEN-II by provocative testing with calcium and/or pentagastrin and measurement of calcitonin²⁶ has led to early detection of microscopic cancer localized to the thyroid gland, which is curable by total thyroidectomy.²⁷ Patients with ZES have a specific circulating serum marker for the disease, gastrin. In addition, the response to secretin is specific and leads to a diagnosis with minimal, potentially surgically curable, disease. In this study, all patients in the operated group had an elevated serum gastrin concentration, and all but one (#30, Table 2) had an abnormal response to secretin.

Potential difficulties with an aggressive surgical exploration for cure of patients with ZES have been described.²⁻⁹ The gastrinomas are not always in the pancreas or any single location so that a simple resection like thyroidectomy for MCT is not possible. The morbidity and possible mortality of pancreaticoduodenectomy (Whipple procedure) or total pancreatectomy is too great for ZES patients who have relatively low-grade, slower-growing, possibly benign tumors. Since gastrinomas are often multiple in the pancreas or in lymph nodes, resection of one tumor does not cure the patient. Gastrinomas can occur as metastases to the liver or lymph nodes at the time of detection. Interestingly, patients with ZES have been biochemically "cured" despite having apparently metastatic liver gastrinomas,²⁵ and lymph node gastrinomas without finding any other primary tumor.^{8,9} The biggest problem in potential gastrinoma resection appears to be inability to find the gastrinoma. In a recent series, approximately 34-40% of patients with biochemical ZES did not have a gastrinoma found at laparotomy.^{9,28} In our study, 38/52 (73%) patients with ZES had gastrinomas found and proven histologically either by imaging studies for patients with metastatic disease or laparotomy for patients with localized disease. This means that 27% of patients with biochemically proven ZES did not have gastrinomas found, despite preoperative transhepatic portal venous sampling, other invasive localization studies, and careful exploration. Scarring from previous abdominal surgery

or total gastrectomy was not a major problem in this series because no patient had total gastrectomy and only 31% of our patients had prior gastric procedures.

In patients with MEN-I, the pancreatic islet cell tumors including gastrinoma are always multiple. A careful examination of the resected pancreas in patients with ZES and MEN-I²⁹ showed that multiple tumors producing multiple, different hormones verified immunohistochemically were present in every patient. In addition, in almost all series, patients with ZES and MEN-I have not been biochemically cured by simple excision of gastrinomas.^{9,28} However, careful follow-up of these patients indicates that the pancreatic islet cell tumors are sometimes as malignant as gastrinomas in sporadic patients.⁵ Patients with ZES and MEN-I may die from metastatic gastrinoma. Therefore, in patients with ZES and MEN-I, we only explore surgically when imaging studies localize a specific tumor mass. Our rationale for removing the tumor mass is solely the malignant potential of the tumor. We do not expect (nor have we) biochemically cured these patients; that is why we excluded them from our "cure" statistics.

A preoperative imaging test that correctly predicted the location of the gastrinoma would assist the surgeon in finding the gastrinoma at surgery. Localization by imaging studies, especially selective arteriography, and infusion CT scanning was an extremely reliable predictor of surgical results, with a positive predictive value of 100%. In contrast, in recent studies of selective venous sampling for gastrin by some,^{10,11,21} but not others,^{30,31} it was frequently positive when no tumor was found.

A preoperative localization study capable of consistently predicting a negative exploratory laparotomy would be highly valuable to identify patients who should not be explored for gastrinoma. Imaging studies like infusion CT and selective arteriogram had a high specificity (100%), but they both had a relatively low-negative predictive value (50% and 60%, respectively). Similar results were reported by Roche et al.³⁰ for selective venous sampling of gastrin in that 44% of patients with a gastrin gradient of more than 50% had no gastrinoma found by the surgeon at laparotomy. The failure of the surgeon to find a gastrinoma does not mean that selective venous sampling is yielding a large number of false-positive localizations, because, when Roche et al. performed blind pancreaticoduodenectomies, small, microscopic gastrinomas were found by pathologists in all cases.³⁰ This resection had a high morbidity and an operative mortality of 37%. In a recent study, no patient with ZES who had a negative laparotomy died from tumor progression when followed for up to 8.5 years after operation.³² Therefore, with the increased ability to control gastric acid secretion medically⁴ and excellent long-term prognosis,³² pancreaticoduodenectomy is contraindicated.

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Imaging studies, especially infusion CT scanning and selective arteriography, were able correctly to identify 70% of extrahepatic gastrinomas, which were subsequently found at exploratory surgery. In addition, selective arteriogram was able to identify 95% of liver metastatic disease, and all of these patients were saved a laparotomy to make the diagnosis because they were all biopsied successfully percutaneously or with a laparoscope. Only one patient was subsequently found at laparotomy to have unsuspected multiple liver metastases. Finally, the high specificity (100% for both infusion CT and selective arteriography) allowed us to tell our patients with certainty that gastrinoma would be found in patients with positive studies. We did not depend on preoperative abdominal ultrasound. It was the least sensitive and had one false-positive (patient #26, Table 5). If we had to choose a study to delete, we would not perform abdominal ultrasound.

What about the patients with negative imaging studies? There were 18 patients with negative imaging studies, and in six patients gastrinomas were subsequently found and removed. Four of six of these patients had very small tumors approximately 5 mm in size, and all were located in stomach, duodenum, or jejunal wall. These tumors were not visible at exploration and were only detectable by careful palpation of these areas. The small size of these tumors and the ability to excise them with normal gut wall around them gave us the hope that a high proportion of these patients would be "cured." In fact, only one patient was "cured" (#5); however, two others (#18, 23) have equivocal results, with abnormal secretin tests but a normal fasting gastrin, and normal secretin tests but abnormal fasting gastrin, respectively. Two patients with negative imaging are most worrisome (#26, 32, Table 5); both had large tumors in the pancreatic tail at the hilum of the spleen. Both patients had histologic features consistent with malignant primary gastrinoma. One patient (#32) had vascular and perineural invasion of gastrinoma with extension outside the pancreas into surrounding tissue; the other patient #26 had extrapancreatic invasion into the spleen itself. In patients with negative imaging, four specific areas appear to be the main possible locations for tumors: the stomach, duodenal or jejunal wall, and the pancreatic tail. We recommend laparotomy for patients without gastrinomas identified on imaging studies, because large, malignant tumors were missed on two occasions and smaller extrapancreatic tumors capable of curative resection were also removed.

The location of gastrinomas resected at laparotomy is illustrated in Figure 2. Stabile et al. have recently identified the gastrinoma triangle as an area in which tumors can be found and potentially removed for cure.³³ This is in contrast to the original descriptions of Zollinger et al.,^{6,7} in which they stated that gastrinomas in the pancreas were in a head:body:tail distribution of 4:1:4.⁷ The anatomic

gastrinoma triangle was defined by the junction of the cystic and common duct superiorly, the junction of the second and third portions of the duodenum inferiorly, and the junction of the neck and body of the pancreas medially, in other words, the area around the pancreatic head. Stabile et al. reported that in 89% of the 32 patients in whom gastrinomas were found, the tumors were located within the confines of this anatomic triangle.³³ In addition, in five patients who were thought to be cured, the tumor was in the anatomic triangle. In our experience, gastrinomas were found in the gastrinoma triangle in 13/20 (65%) of patients in whom tumors were found and nearly half of those patients have demonstrated biochemical "cure." In patients with primary pancreatic tumors, the distribution is 4:1:3 (head:body:tail), nearly identical to the description in Zollinger's experience. In the eight patients with primary pancreatic tumors, five patients had biochemical cure on short-term follow-up, similar to the proportion "cured" with extrapancreatic gastrinoma. This is different from the results of Wolfe et al., which indicated that extrapancreatic, extraintestinal gastrinomas were cured more often than pancreatic gastrinomas.⁸ In our series, the same percentage of patients who had gastrinoma in lymph nodes around the pancreatic head were cured as those who had intestinal or pancreatic gastrinomas.

The ability to "cure" or totally arrest the malignant potential of gastrinomas in patients with ZES is the most important endpoint. Cure has usually been defined in other series as a return to normal basal serum gastrin levels. If we examine the ability of surgeons in previous series to resect gastrinoma and return basal serum gastrin levels to normal, we detect that in the five largest series, 24/149 patients or 16% of patients with ZES were curable.² However, in all of these series, the surgeon performed concomitant total gastrectomy on most patients, except for six patients in whom Deveney was able to resect gastrinomas.⁹ Therefore, these series do not give a true estimate of the possible cure rate by simple enucleation and in fact suggest that it would be much lower than 16%, because in many of the "cures" the gastrinomas were found only by the pathologist and not by the operating surgeon. Therefore, "cure" was serendipitous. Our strategy of performing no antiulcer procedure and concentrating solely on finding and resecting gastrinomas for cure has not been tried by any other group and has never before been performed in a true prospective study. Our initial report of the first seven patients indicated that in three of seven patients we were able to return both basal and secretin stimulated serum gastrin concentration to normal levels. This initial data suggested that "cure" may be achievable in 42% of ZES patients.¹² Subsequently, we have explored 32 patients in the exact same manner, and, when we exclude three patients with MEN-I (who we and others believe are not curable by tumor excision) and the

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one patient who was found to have liver metastases, we examine 28 patients who are potential candidates for surgical cure. Surgical cure is defined as normal basal gastrin concentration, a negative secretin test, and no detectable tumor on imaging studies. Immediately after operation, 12/28 (43%) were found to meet criteria consistent with cure. This is identical to the number predicted (3/7) in our initial report.¹² However, with increasing length of follow-up, true cures were fewer. Figure 3 indicates that secretin tests as well as basal gastrin levels must be followed, to accurately assess recurrent or persistent gastrinoma. One patient initially had both abnormal fasting gastrin and secretin response, which on longer follow-up became normal. However, several patients have subsequently developed elevated basal gastrin levels and/or abnormal gastrin response to secretin consistent with recurrent gastrinoma. This is not surprising when one remembers the malignant nature and multifocal location of these tumors.²⁴ However, this recurrent disease phenomenon has not been clearly described previously, and it underscores the necessity for careful, long-term follow-up with both basal and provocative testing. Subsequent development of abnormal gastrin levels or abnormal secretin tests have limited detectable "cure" rates to 35% at 3 months after operation and 30% with long-term follow-up (mean: 22 months). Whether biochemical recurrence will translate into aggressive metastatic or locally recurrent gastrinoma is not known, and in a recent study no patient with ZES who had a negative laparotomy died from tumor progression when followed up to 8.5 years after operation.³⁴ We have not yet detected recurrent disease or persistent tumor on imaging studies including CT and arteriogram when patients had either negative laparotomy (12 patients) or all gastrinoma resected (19 patients), with maximum follow-up greater than 4 years. The solitary patient who had liver metastatic disease at laparotomy has progressive disease on imaging studies.

Despite the apparent usefulness of infusion CT and selective arteriography to image gastrinomas that were surgically resectable, it must be acknowledged that in the current series of 52 consecutive patients, surgical exploration remained the single most sensitive means of identifying gastrinomas. Surgical exploration identified seven gastrinomas in locations that were not identified by the preoperative imaging studies including liver metastases in one patient, four gut wall tumors, and two pancreatic tail tumors. In addition, it appears that there may be a learning curve in operative identification of gastrinomas, as we have identified tumors in the last six consecutive patients (two patients too recent for inclusion in this report).

In conclusion, this analysis of laparotomy and gastrinoma resection in 32 patients with ZES shows that imaging studies, especially CT and arteriography, but not

ultrasound, are helpful in predicting the location and extent of gastrinoma and should be done before operation on all patients with ZES. A negative imaging result should not be used to determine whether exploration should be done, because in 33% of patients, a gastrinoma will still be found at careful exploration. Exploration and gastrinoma resection can be performed with acceptable morbidity and no operative mortality. Long-term "cure" rate appears to decrease with time, but these results suggest that with our methods a long-term cure rate as high as 30% may be possible.

Acknowledgment

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DISCUSSION

DR. STANLEY R. FRIESEN (Kansas City, Kansas): I want to applaud these authors for developing a prospective study, hoping to pick up those patients in whom tumor excision alone is the object of their study. Unfortunately, this goal is going to exclude patients with hepatic metastases and those patients with multiple endocrine tumors of the genetic variety; but if it does find patients with localized tumor in the duodenum or in the nodes, then the study is worthwhile.

In the last 10 years since I reported our results to this Association, we have also concentrated on those patients with isolated tumors and have found 16 patients now in the entire group: ten with duodenal gastrinomas and six with gastrinomas found only in the lymph nodes in whom excision is all we did. Eleven of these 16 patients were converted to a normal serum gastrin state. This is 69%. This means that 30 or 31% must have had unrecognized tumor or metastases coming on in the future as a recurrence. These recurrences are usually in patients with multiple endocrine adenopathy, Type I.

I have some concern about their finding that 41% (if I read the abstract correctly) had no tumor found at operation in spite of biochemical markers suggesting tumor gastrinoma. I am wondering if they are not overlooking another source of gastrin in those patients.

(Slide) There are patients with elevated serum gastrin concentrations at rather high levels in whom tumor cannot be found but who have antral G cell hyperplasia that is producing their hypergastrinemia. These patients can be picked up before operation by demonstrating a normal secretin test response and by meal stimulation that produces an exaggerated serum gastrin response.

(Slide) I have had 28 patients in whom an antral source of gastrinemia has been found; you will notice that two of those patients had fasting serum gastrin concentrations up around 1000 pg/ml. You would expect them to have tumor gastrinomas ordinarily. They even had false-positive secretin tests before they came to me. When I repeated the tests, you can see that their secretin stimulation did not spike. At operation, no tumor was found, and in all 28 patients the gastrin levels came down to normal after surgical antrectomy with or without vagotomy. I think that in those patients in whom a tumor is not found thus, one should do a vagotomy and antrectomy on the basis that they may have an antral source for their hypergastrinemia.

DR. EDWARD PASSARO, JR. (Los Angeles, California): I greatly enjoyed this presentation because it is another step in the evolving saga of the gastrinoma. We have seen a disease, which was treated initially by total gastrectomy and subsequently managed by H₂ blockers, that is now being cured, potentially, in about one third of its patients, by proper selection. We would agree with the authors that in carefully selected patients, *i.e.*, those without liver metastases and those without MEA, cure should be possible in no less than one third.

Some time ago we described an area where we can find these tumors, and we emphasized that all lymph nodes in that area should be excised, hoping to find tumor within small lymph nodes. My questions to the authors are: How often have they found tumors within that area? What percentage in particular of the occult tumors was found within the area of the gastrinoma triangle, as we have elected to call it? And, in particular, how many cures were possible by excision of tumor within that area?

I noticed that, overall, the localization tests they carried out were effective in about 77% of the patients, and at operation they found about 65% of the tumors (14 of 20). If that is the case, how many of those tumors were found by virtue of having the preoperative localization test done? I think that is really the crux of the problem. How many of those tumors would not have been found had the studies the authors carried out not been done?

DR. JAMES C. THOMPSON (Galveston, Texas): Even though this series of patients has largely been presented before, it is worthwhile listening. The authors have made important observations, as Drs. Passaro and Norton said. If we could actually cure the tumor, then we would be able to defuse both of the threats of this disease, one, the hypersecretion threat and the second, the threat of dying from neoplasia.

The question is: Which gastrinomas can we cure? In our experience, which I believe is exactly parallel to the one in Gainesville, we have been able to cure only those gastrinomas that are both extrapancreatic and extra-GI.

Dr. Norton showed us several tumors (the excision of which led to normal gastrin levels) that were in the gastrointestinal tract alone. I have some concern about that, because we have some experience in which excision of similar tumors has led to normal gastrin levels for a long time, but to our great dismay, a year or more later, the gastrins returned and evidence of tumor activity resumed.

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In one of our patients we found the tumor in his liver. We did an extended right hepatic lobectomy, and his gastrin levels returned to normal. We followed him for more than a year and a half. He contracted a series of severe infections and died with a chlamydial pneumonia and at autopsy was found to our great surprise to have a small primary tumor in his pancreas. We had done a hemipancreatectomy at the original operation. He died with normal gastrin levels, but he did have a residual islet cell tumor.

I would like to ask Dr. Norton about the length of follow-up in these patients, and how many of them in fact have shown evidence of increased gastrin production after having a long period of normal gastrin.

The other problem I would like to address is the dismissal by these authors of the use of total gastrectomy in their introduction as an up-to-date means of treating this syndrome. I would certainly agree that the drugs that are now available are absolutely marvelous. Omeprazole can stop acid secretion in its tracks. However, the problem we have in our everyday patients, who live in Conroe and Dime Box, is that they will go home, leave the hovering care of their concerned gastroenterologist and us, and they will then stop taking their pills. We have problems with patient compliance. Since this is a cyclic disease, they often stop taking their pills and nothing happens. Thus, they stop taking their pills permanently until they are then faced with the vicissitudes of another complication of the disease. For this reason, we have found that total gastrectomy is an amazingly effective treatment because it removes the factor of patient compliance from the therapeutic equation.

That has been our experience. I would suggest that these 52 patients who are being seen by this wonderful group of concerned physicians at the National Institutes of Health may, in fact, when they return home and live in their ordinary environment, stop taking those wonderful pills, and, when they do, I suggest that some of them may get into trouble.

Dr. Jeffrey A. Norton (Closing discussion): Specifically in response to Dr. Jensen, I think your result of 16 normal postoperative basal serum gastrin cases is the highest in the literature and one I would like to achieve.

Approximately 30% of our patients did not have histologically proven tumor found in a combination of laparotomy and radiographic studies. These patients did have meal stimulation studies that were negative, and they all had positive secretin tests; thus, the biochemical diagnosis was still consistent with Zollinger-Ellison syndrome.

In response to Dr. Passaro, 65% of the gastrinomas were found in the gastrinoma triangle that you reported in the *American Journal of Surgery*. These patients did not have a higher cure rate than other patients. Most of these triangle tumors were very small.

How many tumors would have been found without preoperative localization? I was biased by the preoperative localization, and I knew the results and where to look. I think I would have found all the tumors without preoperative localization. There is a learning curve, and I am getting better at it. I have found tumors in the last six consecutive patients.

Dr. Thompson, we agree that we need long-term follow-up of these patients. There were three normal postoperative gastrin levels that increased with long-term follow-up, and this finding suggests recurrent disease.

We do not totally dismiss total gastrectomy. We have demonstrated clearly that total gastrectomy is not necessary. We think that total gastrectomy for the typical patient is not indicated, because we can control ulcer disease medically. If one follows ZES patients very closely, one can control acid output with medication alone. It requires not only seeing the patient but measuring acid output. Our gastroenterologists are committed to this. They do it very well, and we have not had any problems related to ulcers in over 50 patients. Total gastrectomy is another acceptable way to control the ulcer disease in patients with ZES.