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Zollinger-Ellison Syndrome: Past, Present and Future Controversies

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It is fitting that the Zollinger-Ellison syndrome (ZES) be included in the Lester Dragstedt Symposium because Dr. Dragstedt had a long-time interest in this disease, having been one of the five discussants of the original article and subsequently reporting with Dr. Oberhelman on nine cases. The approach to therapy of ZES has been controversial from the beginning, and a number of controversies remain. In this article, four different controversies are analyzed from the prospective of the past (Zollinger-Dragstedt era, 1955-1980), present and what may happen in the future in light of recent results. Specifically analyzed are: 1) the role of gastric surgery in the management; 2) whether gastrinoma removal without aggressive resection in patients with ZES without MEN-I is the preferred surgical therapy; 3) whether patients with MEN-I should undergo routine surgical exploration; and 4) whether most gastrinomas will be localized preoperatively. An analysis of recent advances suggests there may be marked changes in the future from our current and our past approaches.

INTRODUCTION

In 1955, Zollinger and Ellison described two female patients with a syndrome characterized by the presence of primary peptic ulcerations in unusual locations such as the distal duodenum or jejunum, gastric acid hypersecretion of gigantic proportion and the presence of a nonspecific islet cell tumor of the pancreas [1]. It was subsequently shown that this syndrome is due to the autonomous release of gastrin by the tumor and, thus, they were called gastrinomas [2]. A number of other important aspects of the disease have since been recognized [3]. Although older studies suggested gastrinomas were distributed in a 4:1:4 ratio in pancreatic head, body and tail [4], recent studies show that gastrinomas occur primarily (> 80 percent) in the duodenum-pancreatic head area [3, 5-7]. Currently, only 34 percent of patients have metastases at the time of diagnosis [3]; however, older studies suggest that up to 90 percent of gastrinomas are malignant [8]. Approximately 20 percent of patients with Zollinger-Ellison syndrome (ZES)[b] have it as part of the multiple endocrine neoplasia-type I (MEN-I) syndrome [3], which is characterized by autosomal dominant inheritance and hyperplasia or multiple adenomas in multiple endocrine organs (primarily hyperparathyroidism, 95-100 percent; pancreatic endocrine tumors, 82 percent; and pituitary adenomas, 60 percent) [9]. Survival has been shown to be related to control of the gastric hypersecretion, whether MEN-I is present or not, tumor location and tumor extent [3]. The acid secretion can now be controlled with

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[b]*Abbreviations used*: ZES, Zollinger-Ellison syndrome; MEN-I, multiple endocrine neoplasia, type I; BAO, basal acid output; MAO, maximal acid output; ECL, enterochromaffin-like cells; IAS, intraarterial injection of secretin; PVS, portal venous sampling; PPomars, pancreatic polypeptide producing tumors.

Table 1: Lester Dragstedt and Zollinger-Ellison syndrome.

I.	1955	One of the original five discussants of Zollinger and Ellison's original paper [1]. Discussion included a description of one case.
II.	1958	With Drs. H. A. Oberhelman and T. S. Nelson [11] description of two patients with ZES treated with removal of gastrinoma and gastric resection. Case one was one of the first cases of ZES treated by total pancreatectomy.
III.	1961	With Drs. H. A. Oberhelman, T. S. Nelson, and A. N. Johnson [12] reported experience with six cases of ZES. In four of the six cases complete resection of the tumor with reduction in gastric secretion to normal was obtained.
IV.	1966	Experience with nine cases of ZES discussed in a symposium on gastrin [13].

potent antisecretory agents such as H^+/K^+-ATPase inhibitors (i.e., omeprazole, lansoprazole) both short- and long-term in all patients [3, 10].

It is fitting that this disease be included in the Lester R. Dragstedt Symposium because Dr. Dragstedt had a long-term interest in the effect of the pancreas on gastric secretion as well as in the Zollinger-Ellison syndrome (Table 1). He was one of the original five discussants of the 1955 Zollinger and Ellison paper [1], presenting one case of his own and in later presentations of studies done with Dr. Oberhelman, presenting data with eight more cases and pointing out that it was one of the causes for failure of a peptic ulcer to heal after a vagotomy [11-14].

Zollinger-Ellison syndrome has been extensively reviewed recently [3, 15-17]. In this paper, only certain controversial areas of management will be dealt with. Because of the prospective it provides, I have elected to present these as questions analyzed in terms of the past view (Zollinger-Ellison and Dragstedt era, 1955-1980), the view at present and then what may happen in the future.

QUERY I: WHAT IS THE ROLE OF GASTRIC SURGERY IN THE MANAGEMENT OF PATIENTS WITH ZES?

I-A, Past. Initially it was unclear whether attempted curative gastrinoma resection or gastric surgery to remove or alter the responsiveness of stomach should be done [1, 4, 13, 14]. Numerous early studies [3, 4] demonstrated that gastric acid hypersecretion could only be reliably controlled by a total gastrectomy. Some early studies, including a study by Dragstedt, showed that some patients became asymptomatic after resection of the gastrinoma only [11, 18, 19]. However, this treatment course was generally not pursued because in most cases gastrinoma resection did not result in long-term cure, and if the disease recurred, the acid hypersecretion led to life-threatening complications.

I-B, Present. Currently, the reverse situation from the past is recommended. Gastric acid surgery is recommended only in patients who cannot or will not take gastric antisecretory agents [3, 20]. With the recent availability of potent gastric acid antisecretory agents, particularly the H^+/K^+-ATPase inhibitors, omeprazole or lansoprazole, hypersecretion can now be controlled medically (Table 2). The H^+/K^+-ATPase inhibitors have a long duration of action in contrast to the histamine H_2-receptor antagonists, making once

Table 2. Results from studies of long-term medical control of gastric hypersecretion in patients with ZES.

Principal antisecretory drug(s)	No. of[a] patients	Mean Duration of treatment (mo)	% Failure	Author, Year, Reference
Histamine H_2-receptor antagonist				
Cimetidine	13	--	61	Bonfils et al., 1979 [21]
	14	11	0	Stage et al., 1979 [22]
	17	26	65	Deveney et al., 1983 [23]
Cimetidine plus anticholinergic agent	61	12	8	McCarthy, 1978 [24]
	12	33	65	Stabile et al., 1983 [25]
	18	29	6	Malagelada et al., 1983 [27]
Ranitidine	15	18	40	Mignon et al., 1982 [27]
Ranitidine plus anticholinergic agent	19	14	0	Jensen et al., 1984 [28]
Famotidine alone or with anticholinergic agent	32	10	0	Vinayek et al., 1986 [29]
H^+/K^+-ATPase inhibitor				
Omerprazole	40	29	0	Maton et al., 1989 [30]
	80	19	8	Lloyd-Davies et al., 1988 [31]
	31	ND	3	Hirschowitz et al., 1988 [32]
	22	27	0	Bardram et al., 1989 [33]
	20	16	0	Cadranel et al., 1989 [34]
	116	38	0	Metz et al., 1993 [35]
Lansoprazole	21	31	0	Jensen et al., 1993 [36]
	28	18	0	Hirschowitz, 1993 [37]

[a] Only series that include at least 13 patients are included.

or twice a day dosing possible [10]. In contrast to the older studies with histamine H_2-blockers (Table 2) [21-29], gastric acid hypersecretion has been able to be controlled in all patients [30-37]. A recent study reports omeprazole also is effective long-term with patients treated up to nine years without loss of control or toxicity [35]. Furthermore, a recent study demonstrates the daily dose of omeprazole can be reduced to the same dose used in patients with idiopathic duodenal ulcer disease (i.e., 20 mg., daily) in 95 percent of patients with uncomplicated diseases (no MEN-I, previous gastric surgery or severe reflux disease) [38]. Therefore, at present, oral gastric antisecretory agents are convenient and effective in all patients who will take the medication, and total gastrectomy is not recommended.

I-C, Future. It is likely that in the future two forms of gastric surgery may be important in the management of patients with ZES. A recent study (Figure 1) demonstrates that postcurative gastrinoma resection, BAO and MAO decrease within three to six months by 75 percent and 50 percent, respectively [39]. However, long-term (up to four years) 67

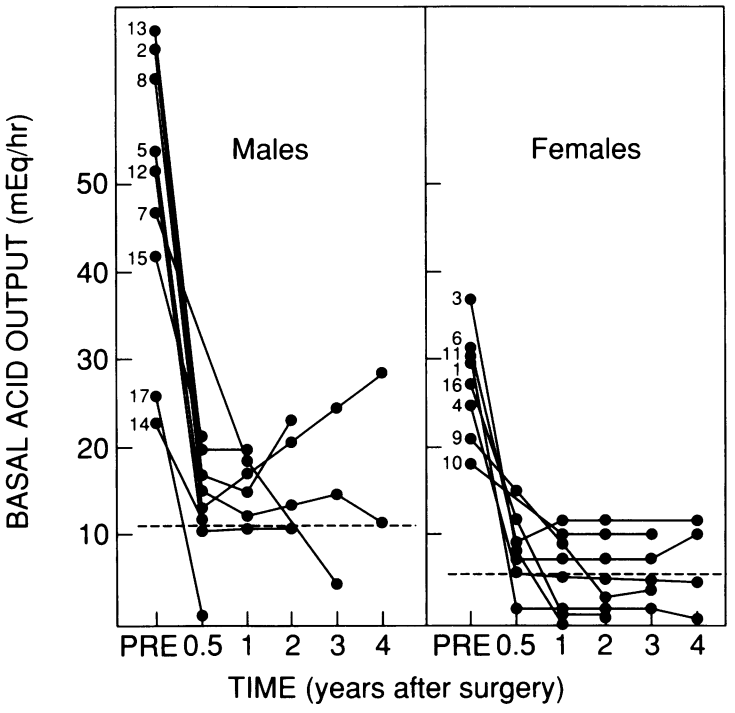

Figure 1. Effect of curative gastrinoma resection on basal acid output. Basil acid output (BAO) was measured before and up to four years after curative resection of 17 patients. Data for men (n=9) and women (n=8) are shown in the left and right panels, respectively. The dotted line represents the upper limit of normal for BAO for men (10 mEq/hr) and women (5.6 mEq/hr). Data are from Ref. 37.

percent of patients remained mild gastric hypersecretors, and 40 percent required low doses of ranitidine [39, 40]. Routine parietal cell vagotomy for patients with ZES has been recommended in the past [18]; however, a number of authorities have questioned this [1, 20], and it is now infrequently performed. A recent preliminary report of the patients in the above study [41] showed, on long-term follow-up (average, 10 years) post-parietal cell vagotomy, that these patients without tumor resected show an average decrease of 75 percent in basal acid output. If the routine addition of parietal cell vagotomy to curative gastrinoma resection could be shown to result in most patients not requiring any gastric antisecretory drug, then this procedure may be routinely performed in those patients undergoing exploration for possible gastrinoma resection in the future.

Recent studies in animals demonstrate that chronic hypergastrinemia causes increased numbers of gastric enterochromaffin-like cells (ECL cells) and a progression in changes in ECL cells from hyperplasia (simple diffuse to linear, to micronodular, to adenomatoid) to dysplasia and finally to the carcinoid stage. Some gastric carcinoid tumors are malignant [3, 42-44]. Previous studies have reported gastric carcinoid tumors in patients with ZES and that the ECL cells are increased, usually two- to three-fold [43, 45, 46]. In a recent study of patients with ZES without MEN-I, ECL cells showed a normal pattern in 16 percent of patients; 71 percent showed a simple diffuse hyperplasia; and 13

percent showed a linear hyperplasia [47]. In patients with ZES with MEN-I, 53 percent showed diffuse hyperplasia; 47 percent showed linear hyperplasia; and six percent had areas of dysplasia [47]. Until recently, most patients underwent total gastrectomy, so that there are only limited numbers of patients to assess the long-term risk of developing gastric carcinoid tumors. However, with the availability of potent oral gastric antisecretory agents, two groups have recently reported such data. In patients with ZES and without MEN-I, in one study from the NIH of 160 patients, 0.6 percent (one patient) had a gastric carcinoid [46]; whereas in the other study (31 patients), 0 percent had a gastric carcinoid [47]. In contrast, in patients with ZES with MEN-I, in one study from the NIH of forty patients, 13 percent had gastric carcinoids [46]; whereas in the other study (17 patients), 30 percent had gastric carcinoids [47]. An additional single patient with ZES without MEN-I with a gastric carcinoid tumor has been reported [48]. These data demonstrate that gastric carcinoids occur in both patients with ZES with or without MEN-I and that genetic factors are important in determining the frequency. In a patient with ZES without MEN-I, the risk appears to be quite low; whereas in patients with ZES with MEN-I, it is at least 30-fold higher. Recent genetic studies show allelic loss on chromosome 11q13 in parathyroid and pancreatic tumors in patients with MEN-I [49, 50], suggesting the MEN-I gene functions as a tumor suppressor gene. Furthermore, a recent study shows loss of heterozygosity in a gastric carcinoid tumor from a patient with MEN-I [51], suggesting these tumors result from inactivation of two copies of the MEN-I gene, providing a basis for the genetic contribution to gastric carcinoids in these patients. It has been estimated that 10 percent of these gastric carcinoid tumors in hypergastrinemic patients are malignant [44]; however, this is based on small numbers of patients with limited follow-up. At present, the true percentage of patients with ZES who develop gastric carcinoids or the percentage malignant is unclear. This has occurred because of the small numbers of patients evaluated and because it is unclear what percentage of these tumors are detected or the extent of invasiveness evaluated by routine endoscopy and biopsy. With total gastrectomy now not routinely done, increasing numbers of patients with ZES will be found to have gastric carcinoids and in the future it is likely that surgical resection of some of these will be increasingly considered. It will need to be defined how frequently they are malignant and at what state surgical resection should be considered.

In summary, in the future it is likely a group of patients will be defined who will benefit from routine parietal cell vagotomy, and gastric surgical procedures may be needed for some patients with gastric carcinoid tumors.

QUERY II: WILL GASTRINOMA REMOVAL WITHOUT AGGRESSIVE RESECTION (WHIPPLE'S) BE THE OPERATION OF CHOICE IN PATIENTS WITH ZES AND WITHOUT MEN-I?

II-A, Past. As discussed in I-A., in early studies, curative resection of the gastrinoma was rarely accomplished [5-7, 22, 26, 52-59] (Table 3). Furthermore, because of the need to adequately control the gastric hypersecretion, total gastrectomy was the primary procedure done, and the tumor resection received less emphasis [4]. Two exceptions to this are the 25-year results of Friesen reported in 1982 [60] and the studies of excision of duodenal gastrinomas reported by Oberhelman in 1972 [19]. Friesen reported a relatively high

Table 3. Percentage of patients with Zollinger-Ellison syndrome surgically cured in different series.

No. of patients[a] operated	Percent with normal serum gastrin postoperatively	Author, year, reference
25	4	Stage et al., 1979 [22]
42	5	Zollinger et al., 1980 [53]
32	6	Bonfils et al., 1981 [54]
28	22	Wilson et al., 1982 [55]
26	12	Thompson et al., 1983 [56]
52	12	Deveney et al., 1983 [52]
44	16	Malagelada et al., 1983 [26]
45	11	Stabile et al., 1984 [5]
29	43 (immed. post op)[b] 30 (6 mo-4yr)	Norton et al., 1986 [6]
125	26	Mignon et al., 1986 [57]
60	17	Ellison et al., 1987 [58]
43	27	Delcore et al., 1989 [59]
73	58 (3 mo)[b]	Norton et al., 1992 [7]
73	30 (5 yr)	

[a] Included are the results of attempted surgical cure from series with at least 25 patients undergoing surgical exploration.
[b] Refers to time of evaluation postoperatively.

rate of 39 percent having normal fasting gastrins postresection [60] in 23 patients undergoing total gastrectomy and removal of all resectable tumor. However, it is not apparent how many of these patients had serial provocative tests and how long the follow-up was in each patient. Oberhelman [19] reported follow-up in 11 cases with duodenal tumors all treated by tumor excision and only one patient also undergoing total gastrectomy. Excellent symptomatic results were maintained for two to 11 years without a need for total gastrectomy.

II-B, Present. At present, removal of the tumor by enucleation in the pancreatic head, resection, or enucleation in the pancreatic body or tail and resection in the duodenum is the recommended procedure of choice for patients with ZES without MEN-I [3, 61]. The role of a Whipple procedure at present is controversial. Because of the excellent long-term prognosis of patients even with lymph node metastases [62, 63], it is, at present, not generally used. However, some groups are increasingly considering it, especially in selected patients with ZES and MEN-I [64-66] who have a family history of aggressive disease and frequently have multiple gastrinomas in the duodenum. Results of recent series report cure rates significantly better than the 12-25 percent reported in the past with some series reporting rates greater than 50 percent (Table 2).

II-C, Future. A number of points suggest that in the future the approach may be different from the present. First, the true long-term cure rate is at present not clear and is likely significantly lower than a number of the studies in Table 2 suggest [6, 7, 57-59]. A recent study [67] demonstrates that to detect all recurrences after resection, both fasting gastrins and secretin provocative tests must be performed on a regular basis because neither alone detected all recurrences. Furthermore, in many of these studies, the follow-up time is relatively short, and a recent NIH study shows that there is a steady relapse rate up

Table 4. Preoperative localization of the gastrinoma in patients with Zollinger-Ellison Syndrome.

	% Positive in recent NIH surgical series[a] (range in other series)[b]	
	All Patients	Duodenal Gastrinomas
Imaging Study:		
Ultrasound	19 (21-28)	4
CT scan	28 (35-59)	12
Angiography	59 (35-68)	46
MR imaging	25 (21-25)	20
Functional Study:		
Portal venous sampling	73 (46-94)	77

(a) % Positive in Recent NIH Surgical Series refers to the percentage of patients considered for surgical exploration (no liver metastases) in which the indicated test was positive. From Refs. 3, 6, 67-79, 72, 84-88

(b) Range of results reported in various series. From Refs. 3, 6, 7, 83, 87.

to five years [7]. The NIH study involving 73 patients reported in 1992 [7] is both long-term (up to nine years), and both fasting gastrin and secretin provocative tests were performed yearly in all patients. This study [7] demonstrated an immediate postoperative normalization of serum gastrin and secretin tests in 58 percent of patients and a five-year cure rate of 30 percent. These data suggest that at present less than one-third of patients are cured long-term, and if it is to be improved in the future, it is likely the surgical approach may have to be modified. Second, a recent NIH prospective study demonstrates that with the use of routine duodenotomy an additional 56 percent more duodenal tumors can be detected than with the use of palpation after duodenal Kocherization and operative ultrasound [68]. However, even with the use of all procedures including duodenotomy, which resulted in finding tumors in 93 percent of all patients, the immediate postoperative cure rate increased only slightly (i.e., from 50 to 62 percent) [7]. One important reason for this minimal increase in patients without any evidence of disease immediately postresection was that the increased numbers of tumors found were due to increased numbers of duodenal tumors [7]. In contrast to older studies that suggested these were more frequently benign than pancreatic tumors, 55 percent of all the duodenal tumors had metastases to regional lymph nodes [3, 7, 60, 68, 69]. These results suggest that the older concept of duodenal gastrinomas being entopic and less malignant whereas pancreatic gastrinomas are ectopic and more frequently malignant is not correct [3, 69-71]. Third, even though the duodenal tumors have at least as high a metastatic rate to lymph nodes as pancreatic gastrinomas, their metastatic rate to the liver is low [69].

With the high frequency of local lymph node metastases with duodenal tumors resulting in a 30 percent long-term cure by simple resection, it is likely in the future increased consideration of a Whipple procedure in selected cases will occur. This approach will be further considered because of the sensitivity of functional localization studies such as percutaneous transhepatic sampling for gastrin concentrations of portal

venous tributaries or the newer technique of hepatic venous sampling for gastrin content after selective intraarterial secretin injections [66, 72]. This latter technique has proved very sensitive for localizing gastrinomas to the pancreatic head/duodenal area [72] (Table 4, Figure 3). Therefore, if only a positive lymph node is found in the pancreatic head area at surgery as occurs now in 20 percent of all cases, coupled with functional localization, there will likely be an increased tendency to do a Whipple procedure. Already a few groups have advised it be considered in similar situations [64-66]. At present, with the available data, such an aggressive approach is unwarranted. Patients with only lymph node metastases have an excellent long-term survival that is not significantly different from that in patients with completely resected tumors in a number of studies [62, 63]. For a Whipple procedure to be recommended, it needs to be shown that the performance of a Whipple operation can improve survival rate, or a subgroup of patients with a worse prognosis needs to be identified in which this operation could be justified. A recent DNA flow cytometry study [73] demonstrates that the DNA pattern seen is an independent predictor of tumor behavior. However, flow cytometry needs to be done in more patients to verify its predictive value. If verified, a method would have to be developed that would allow flow cytometry to be used as a rapid procedure in the surgical setting. Additionally, if either serological or tissue predictors of poor prognosis can be identified, then the appropriateness of such aggressive surgery may be justified.

In summary, in the future it is likely even more aggressive surgery will be indicated on a subset of patients.

QUERY III: SHOULD PATIENTS WITH ZES WITH MEN-I UNDERGO ROUTINE SURGICAL EXPLORATION FOR POSSIBLE CURE OF THE GASTRONOMA?

III-A, Past. Although the MEN-I syndrome was described in 1954, this syndrome was reported in 1964 in a review of 260 patients with ZES to occur in only 3 percent [4]. It is now clear that at least one of the two original patients with ZES reported by Zollinger and Ellison [1] had ZES with MEN-I because one patient had a sister with an insulinoma. Subsequent studies clearly demonstrated that MEN-I syndrome occurs in approximately 20 percent of patients with ZES. In the past, the presence of MEN-I did not significantly change the surgical management because all patients underwent total gastrectomy and in some centers, simultaneous excision of all resectable tumor whether MEN-I was present or not.

III-B, Present. At present the role of surgery to possibly cure patients with MEN-I is controversial. In the last 10 years, it became increasingly clear from a number of surgical studies that patients with ZES with MEN-I were not cured by simple tumor enucleation [3]. In one review, 0 of 37 cases were cured by simple tumor enucleation [74]. Pathology studies demonstrated that these patients frequently had multiple small microscopic adenoma in addition to large tumors, and this failure to cure these patients was thought due to an inability to remove all microadenomas that might be secreting gastrin [74, 75]. It was therefore suggested by most investigators that these patients not undergo routine laparotomy for cure. Additional data used to support this conclusion were that, in some studies, these patients had a significantly better prognosis than patients without MEN-I [3]. Although in the past a localized gastrin gradient by selective portal venous sampling or

elevated serum pancreatic polypeptide level had been reported to be useful in identifying patients to explore, recent studies show these investigations are not helpful [3, 76, 77]. At present most groups recommend that patients with MEN-I with ZES not undergo routine attempts at curative resection; however, some recommend it be done in selected patients and an occasional group [78] suggest all such patients should be considered for curative resection.

III-C, Future. In the future, the approach of not routinely exploring these patients for possible cure may change. A recent study [78] reported that of eight patients with ZES and MEN-I, gastrinomas were found in the proximal duodenum in all. In three patients solitary tumors were present; in five patients multiple microadenomas were found; and in four patients paraduodenal lymph nodes were involved. In contrast, only one of the seven tumors found in these patients in the pancreas stained for gastrin. In four of six patients the gastrin values returned to normal postoperatively, and these patients were thought cured [78]. This study raises the possibility that the gastrinoma is almost always in the duodenum and potentially curable. It therefore raises the question of whether these patients should thus also undergo routine surgical exploration. It is not apparent from this study that these patients can be cured by simple enucleation of duodenal tumors because two of the four patients with normal gastrins were post-Whipple resection. Furthermore, it is not apparent the patients were actually cured by the procedures done or for how long they were cured. Secretin provocative tests were not performed on these patients. A number of patients have been reported with normal fasting gastrin concentrations postoperative, but with secretin provocation, the presence of a gastrinoma can be determined [67]. The patients in this study did not have secretin tests routinely and regularly performed after surgery. Lastly, many of these patients underwent parathyroidectomies (seven of the eight), and an effective parathyroidectomy has been shown to decrease fasting gastrin values to normal and even cause the secretin provocative test to revert to normal in selected patients with MEN-I and ZES [79]. Furthermore, studies by others have shown a higher percentage of the pancreatic tumors staining positively for gastrin [75, 80]. These results raise the possibility that these patients will not be curable without a Whipple resection because of the multiple tumors and frequent metastases to lymph nodes (at present, as discussed in II-C). Future, it is not established that this procedure will improve survival.

Two additional points are likely to be important in the future in determining whether surgical exploration should be undertaken. First, patients with ZES with MEN-I have a 30-fold higher incidence of gastric carcinoid tumors, and it is likely that both the genetic factors (loss of heterozygosity of the MEN-I locus on chromosome 11q13 in gastric carcinoid tumors) and hypergastrinemia are contributing. If these gastric carcinoids are found to be more malignant than the 10 percent proposed on studies from a small number of patients [44], then the importance of rendering these patients normogastrinemic may increase. Second, recent studies suggest that pancreatic endocrine tumors in patients with MEN-I with ZES are not less malignant than in patients with ZES without MEN-I [3]. Therefore, increasingly in these patients, long-term survival will require treatment of the tumor itself. One study has suggested that patients with pancreatic endocrine tumors undergo exploration and enucleation of the tumors if they are imaged and larger than 2.5

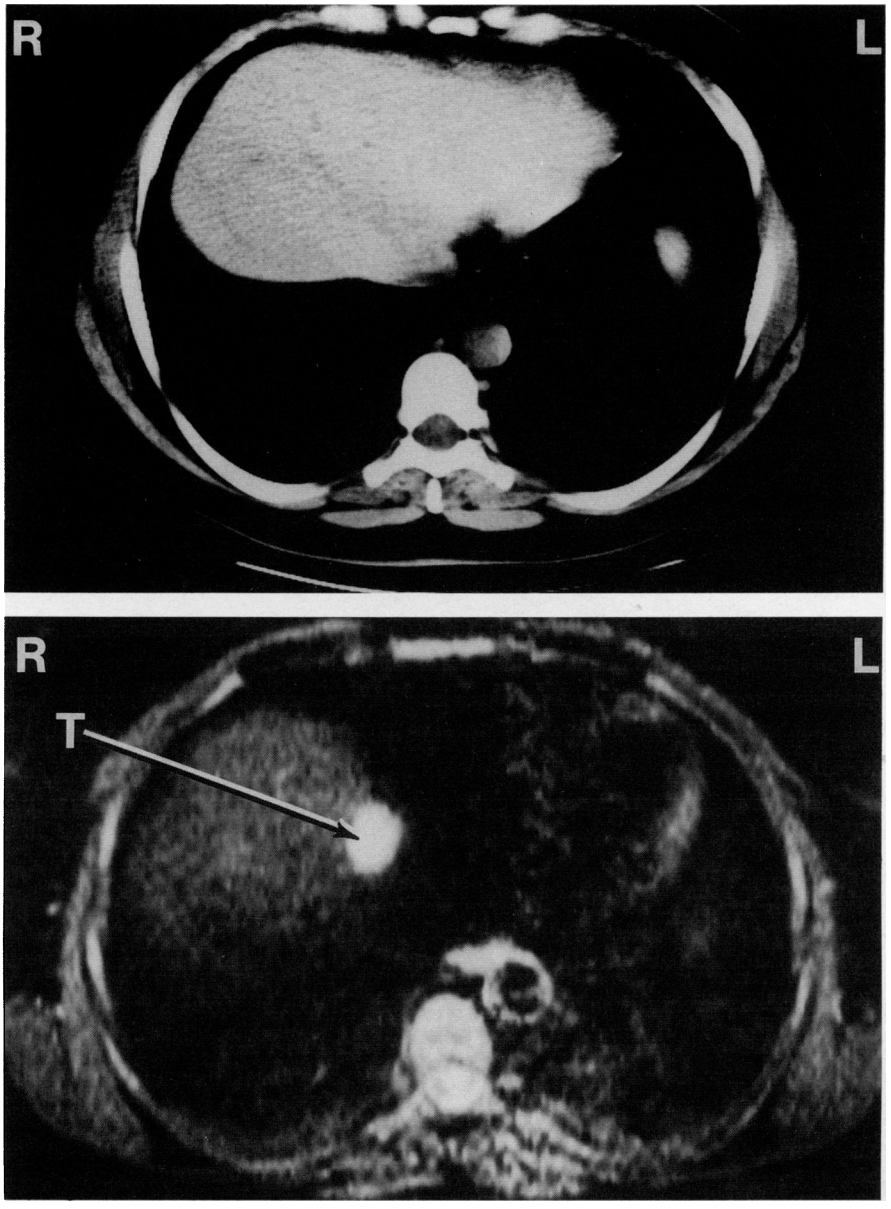

Figure 2. Comparison of the Ability of CT scanning (top panel) or MR imaging (STIR sequence) (lower panel) to localize gastrinoma metastatic to the liver in a patient with Zollinger-Ellison syndrome. CT scanning did not demonstrate any metastatic lesions in the liver, whereas the STIR sequence (MR imaging) demonstrates a metastasis in the left lobe. Abbreviations: T, tumor.

to 3 cm [77]. Using this approach, three of six patients explored were found to have malignant tumors although in no case was the patient cured of the ZES postresection [77]. This approach is based on the premise that pancreatic endocrine tumors are histologically and pathologically indistinguishable from carcinoid tumors, and in a number of tissues, the malignant potential of carcinoid tumors has been shown to be dependent on the size of the tumor [9]. No such data yet exist for pancreatic endocrine tumors. However, because these patients all have numerous microadenomas, it is not possible to completely remove all adenomata without a total pancreatectomy. To routinely operate and even possibly cure the ZES by a lesser operation may not extend life because many of the other tumors that exist in other parts of the pancreas, such as pancreatic polypeptide producing tumors (PPomas), are also frequently malignant [81]. While a total pancreatectomy [82] has been performed in an occasional patient with a family with a poor prognosis, it is not generally recommended. The strategy to use in treating other common pancreatic endocrine tumors that these patients develop, such as PPomas or nonfunctioning endocrine tumors [9, 81], is even less clear than that used to possibly treat the gastrinoma.

In the future, it is likely it will be clearly defined whether patients with MEN-I with ZES will be cured by enucleation of duodenal gastrinomas. It is also likely that subsets of patients may be identified who could benefit by surgical exploration.

QUERY IV: WILL MOST GASTRINOMAS BE LOCALIZED PREOPERATIVELY BY IMAGING OR OTHER LOCALIZATION STUDIES?

IV-A, Past. In the past, the primary tumor was almost never localized by upper GI X-rays or by the limited localization methods available [4]. Ultrasound, arteriography, and later, CT scanning localized a small number of the primary tumors [3].

IV-B, Present. The present abilities of various methodologies to localize the primary gastrinoma are summarized in Table 4. Even though the angiography is reported positive in up to 68 percent of cases and CT scan in 50 percent in various series, at the NIH, the CT scan is positive in only 28 percent and angiography in 59 percent of patients undergoing laparotomy (Table 4). In many cases, these results do not present true localization of the primary tumor because they are not identifying the primary tumor but instead, lymph node metastases, particularly in the pancreatic head area. In a recent study the combination of ultrasound, CT scan and angiography localized a tumor in 52 percent of the cases [7]. However at surgery, 20 percent of the patients had only gastrinoma found in lymph nodes. Furthermore, duodenal gastrinomas are usually less than 1 cm in diameter [7, 69, 83], and imaging studies usually do not localize tumors of this size [84, 85] (Table 4). Of these studies, selective angiography remains the procedure of choice to localize the primary tumor [3, 84, 86]. For the primary gastrinoma, MR imaging, with or without gadolinium, is equally sensitive to ultrasound but significantly less sensitive than angiography [86] (Table 4).

Functional localization by portal venous sampling (PVS) and the newer technique of hepatic venous sampling for gastrin levels after intraarterial secretin injection localize almost 90 percent of all gastrinomas [69, 87, 88] (Table 4, Figure 3). A typical example of both studies in one patient is shown in Figure 3. The portal venous sampling demonstrates a positive gastrin gradient of 1100 percent in the pancreatic head area. Hepatic venous

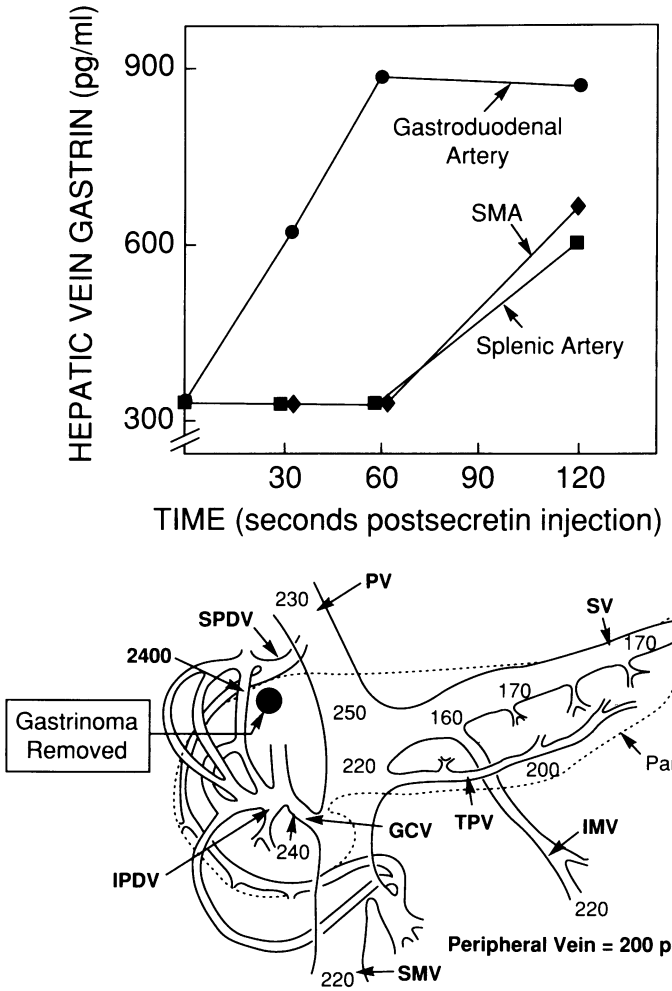

Figure 3. Ability to functionally localize the gastinoma by determination of serum gastrin gradients after intraarterial secretin injection (top panel) or transhepatic portal venous sampling (bottom panel). Top panel: Hepatic venous samples were obtained before 30, 60 and 120 sec after the selective injection of secretin (30 units) into the gastroduodenal, superior mesenteric and splenic artery. A positive gradient (≥50% at 30 sec ≥100% at 60 sec) [68] is seen only with the gastroduodenal injection localizing the tumor in the pancreatic head/duodenal area. Bottom panel: Results are from the same patient as in the top panel. Values are the serum gastrin concentration at the indicated location with a simultaneous peripheral venous value of 200 pg/ml. A positive gastrin gradient [83, 84] of 1100% = [(2400-200/200]x100 exists in the superior pancreaticoduodenal vein draining the pancreatic head area [83]. In the area indicated by the black dot, a 0.5 cm gastrinoma was was found. Abbreviations: PV, portal vein; SPDV, superior pancreaticoduodenal vein; IPDV, inferior pancreaticoduodenal vein; SMV, superior mesenteric vein; GCV, gastrocolic vein; TPV, transverse pancreatic vein; SV, splenic vein; SMA, superior mesenteric artery.

sampling after selective intraarterial injection of secretin (IAS) demonstrates a positive increase only after injection into the gastroduodenal artery which serves the pancreatic head area. At surgery, this patient had a 0.5 cm duodenal wall tumor. In a recent comparative study [72], the IAS was more sensitive than PVS and was particularly sensitive in

patients with duodenal tumors, with 80 percent of patients with duodenal tumors having a positive gastroduodenal injection with IAS and only 30 percent of the patients having a positive PVS. Unfortunately, these functional localization studies only localize to the area (i.e., pancreatic head/duodenum, body, tail) and do not discriminate exactly where in the area the tumor is. Nevertheless, these studies may be useful in the future if a Whipple procedure is being considered.

In contrast to the primary tumor, almost all patients with metastatic disease to the liver can be recognized by a combination of imaging studies [3, 84]. In one prospective study [84], the combination of CT scanning and angiography identified greater than 95 percent of patients with metastatic liver disease. A recent study [86] demonstrates that recent improvements in MR imaging have greatly improved its sensitivity, such that it now has an even greater sensitivity than angiography (83 percent vs. 61 percent) in identifying liver metastases. The metastases are particularly well seen on the STIR (short-term inversion recovery magnetic resonance image) [86] as shown in Figure 2. In this patient the hepatic metastasis was not seen on CT scan (without [Figure 2, top], or with intravenous contrast); however, it was easily seen with the STIR MR image (Figure 2, bottom).

Therefore at present, imaging studies (CT, ultrasound, MR imaging, angiography) localize less than 50 percent of primary gastrinomas and miss most small duodenal gastrinomas (Table 4). Functional localization studies (i.e., venous gastrin sampling) localize more frequently (Table 4) but are only region-specific (i.e., pancreatic tail, head, etc.) [87, 88]. For metastatic gastrinoma to the liver, imaging studies, especially MR imaging in combination with the other studies, will localize almost all patients with liver metastases. Thus, there is a need for better localization studies particularly for the primary tumor. Recently, newer techniques have been described such as endoscopic ultrasound [89, 90], MR imaging with dynamic gadolinium enhancement and fat suppression [91] and radionuclide scanning after injection of radiolabeled octreotide, a somatostatin-octapeptide analogue [92, 93]. These will be dealt with briefly in the next section.

IV-C, Future. In the future, the newer techniques of endoscopic ultrasound, the use of radiolabeled somatostatin analogues and improved MR imaging may enhance preoperative localization. Endoscopic ultrasound has recently been seen to be particularly sensitive for localizing pancreatic endocrine tumors [89, 90]. In one study of 31 patients with various pancreatic endocrine tumors with negative CT scans and ultrasound studies, endoscopic ultrasound localized 82 percent of the tumors found at surgery. Endoscopic ultrasound was also significantly more sensitive than angiography (82 percent vs. 27 percent) [89]. However, as pointed out in an editorial to one of these studies [94], it is not clear that this technique will localize small duodenal gastrinomas. Furthermore, its true false-positive rate has not been carefully studied. Nevertheless, the current data suggest endoscopic ultrasound will localize most pancreatic gastrinomas and may replace some of the other older imaging studies.

Pancreatic endocrine tumors as well as a number of other tumors (breast cancer, small cell lung cancer, CNS tumors, lymphomas) frequently possess high densities of somatostatin receptors that can be used to localize these tumors [92, 95-100]. Both [^{125}I-Tyr^{3}] octreotide and [^{111}In-DTPA-DPhe^{1}] octreotide have been used for localization

[97]. Radiolabeled octreotide scanning has been reported to localize pancreatic endocrine tumors not identified by other methods [92]. In one comparative study of 23 patients with sporadic gastrinoma without known metastases by other localization methods, radiolabeled somatostatin scintography demonstrated in 52 percent of patients areas of increased uptake at sites not known to contain tumors [100]. It is reported to localize the pancreatic primary tumor and their metastases in 80 percent of cases [93]. In another recent study, it localized gastrinomas in all 13 patients studied and was more sensitive than other imaging studies [101]. However, at present, experience with this technique is limited to a few centers and it has not been prospectively studied carefully. It is likely it will prove particularly useful for identifying metastases to bone or lymph nodes in areas that might not ordinarily be carefully imaged. This would suggest it may be particularly important to assess disease extent. Its role in localizing small duodenal gastrinomas at present is unclear.

The sensitivity of MR imaging for pancreatic endocrine tumors is rapidly increasing with recent improvements. A recent study compared MR imaging results in 1993 to MR imaging results from 1985-1987 [86] in patients with ZES at the same institution and demonstrated that the sensitivity for detection of hepatic metastases had increased to 83 percent from 43 percent. This study [86] concluded that MR imaging was now the imaging procedure of choice for identifying hepatic metastases. In this study [86] the sensitivity for primary gastrinomas did not change (25 percent, 1993 vs. 20 percent, 1985-1987). However, another recent study [91] in 11 patients with pancreatic endocrine tumors reported localization with MR imaging with dynamic gadolinium enhancement and fat suppression in all patients. Two tumors (a gastrinoma and insulinoma) were less than 1 cm in diameter and detected by this methodology [91]. These results suggest further improvements in MR imaging may lead to increased sensitivity for detection of even small gastrinomas in the future.

In summary, these preliminary results suggest that the ability to detect primary gastrinomas preoperatively will continue to improve in the future, although it still remains unclear whether any of these procedures has sufficient sensitivity to detect small duodenal gastrinomas.

V. OTHER QUERIES

There are a number of additional queries that could have been dealt with but will be only briefly discussed here.

V-A, Will the time to diagnosis improve further and result in increased survival? In recent studies [3], the time from the onset of continuous symptoms to diagnosis remains five to six years. At present, 34 percent of patients have metastatic disease to the liver at the time of diagnosis [3]. This latter group of patients has a poor prognosis [3], and therefore, if survival is to be markedly improved, earlier diagnosis is needed. Understanding of the natural history of gastrinoma is limited, and it is not clear whether even earlier diagnosis will recognize more patients without metastatic disease. A recent study [58] suggests this will be possible because 56 percent of patients seen at one center before gastrin RIA's had liver metastases and only 23 percent after their introduction. Furthermore, the cure rate increased from four percent to 30 percent, suggesting an earlier state of disease

was being seen. With increased awareness of the disease it would be hoped earlier diagnosis may occur. However, potent gastric antisecretory agents such as omeprazole may actually delay the diagnosis. Omeprazole will control gastric acid secretion in most patients with ZES with the recommended doses used for idiopathic peptic ulcer disease and thus, the response to antisecretory therapy will not be a discriminating feature as it was with histamine H_2-receptor antagonists which did not control gastric secretion adequately in ZES patients with conventional doses [28, 102].

V-B, Will a group of patients having only lymph node primary gastrinomas be identified? At present, approximately 20 percent of patients are found to have gastrinoma only in lymph nodes, usually in the pancreatic head area [7]. A number of these patients in different studies [5, 7, 55, 60, 63, 65, 83] have had long-term cures postresection, and it has raised the possibility that gastrinomas may originate in lymph nodes in some cases. The cell of origin of gastrinomas remains unclear, and therefore at present, this issue remains controversial. With more extensive surgery and additional insights into the cellular origins of gastrinomas, this issue will likely become clearer in the future.

V-C, How will patients with advanced disease with liver metastases be more effectively treated in the future? The current recommended treatment is chemotherapy with streptozotocin and doxorubicin with or without 5-fluorouracil [3, 9, 103]. At present, the true response rate in metastatic gastrinomas and its benefit remain not completely clear. In a study [103] of patients with metastatic disease due to different types of endocrine tumors including gastrinomas, 69 percent of patients responded to streptozotocin plus doxorubicin and 46 percent to streptozotocin plus fluorouracil ($p = .05$) and the length of time to tumor progression was longer with streptozotocin and doxorubicin (median 20 vs. 6.9 mos, $p = .001$). Streptozotocin plus doxorubicin in this study [103] also had a significant survival advantage. However, in two other studies entirely on patients with metastatic gastrinoma, the response rate was five percent with streptozotocin and fluorouracil in one [104] and 40 percent with streptozotocin, fluorouracil and doxorubicin in the other [105] and did not result in increased survival in responders versus nonresponders in one study [105]. Furthermore, this chemotherapeutic regimen is associated with significant toxicity, especially streptozotocin-induced nephrotoxicity. Treatment with α-interferon has been reported to be effective in patients with gastrinomas and other metastatic islet cell tumors [9, 106]. However, in a recent prospective study [107] in 13 cases with metastatic gastrinoma, no patient had a decrease in tumor size; in 30 percent, the tumor remained stable for a variable time, and it was concluded that α-interferon alone was not of benefit in these patients. The somatostatin analogue, octreotide, has also been reported to be useful in endocrine tumors, particularly carcinoid tumors which histologically resemble gastrinomas [9]. However, a preliminary report [108] from a large European study reports that octreotide did not decrease metastatic tumor size in any of the 25 patients treated (including six with metastatic gastrinoma). In this study, 20 percent of patients were considered responders because they demonstrated no tumor growth on octreotide, whereas tumor growth was documented prior to starting octreotide. It therefore appears as a single agent octreotide will be of limited utility.

Increasingly, patients with metastatic endocrine tumors are being evaluated for hepatic transplantation. With increased ability to stage metastatic disease with octreotide scanning and other localization studies, it may be that a subset of patients can be identified where this procedure will be of value in the future.

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