Primary Peptic Ulcerations of the Jejunum Associated with Islet Cell Tumors

Twenty-five-year Appraisal

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A review of 42 patients with gastrinoma, who either survived five years or longer or who died during this period of evaluation, was carried out to define the surgical principles which might be combined with the recent trend toward cimetidine therapy. Thirty-four (80%) of the patients had total gastrectomy with an operative mortality rate of 2.3%, and eight patients (20%) had less than total gastrectomy. No tumor was found in six patients with hypergastrinemia and an abnormal secretin bolus whose five-year survival rate was 100%. Of the thirty-six patients having tissue proof of gastrinoma, twenty-two (61%) had complete resection of all gross tumor resulting in a 76% five-year survival rate. Fourteen patients had unresectable tumor or partial resection with a five-year survival rate of 21%. Complete gross tumor resection increased mean survival by six years ($p < 0.01$), but resulted in persistent eugastrinemia in only two patients. Long-term survival was possible with a combination of vagotomy, lesser gastric procedures, tumor resection, and cimetidine, seven of eight patients living more than five years. Surgical management of gastrinoma should be directed toward aggressive tumor resection and vagotomy, with reliance on cimetidine therapy postoperatively to control the gastric hypersecretion. Total gastrectomy should be reserved for cimetidine failures and those who do not wish to take cimetidine for the rest of their lives.

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OVER THE PAST 25 YEARS, the primary goal in the treatment of gastrin-producing islet cell tumors[1] has been to completely control the hormonally induced gastric hypersecretion by total gastrectomy or the removal of all tumor. Recently, it has been established that gastric secretion can be controlled by the H_2 receptor antagonists, giving the surgeon a greater opportunity to attack the tumor and its metastases. More than one form of therapy is now available, and this has introduced some differences of opinion concerning the management of patients with gastrinoma.

An appraisal of the therapeutic alternatives will be presented, based on 25 years of precimetidine experience with patients with gastrinoma, combined with current concepts gained from the literature and personal impressions of a few authorities in this field.

Clinical Experience

Only the 42 patients who survived five years or longer or who died within the period of this evaluation are included in this report. Such long-term follow-up is essential, since the serum gastrin levels following a surgical procedure may be temporarily lowered, resulting in a false interpretation of the effectiveness of the procedure (Fig. 1). All 42 patients were operated on in the precimetidine era, and more than one-half (25 patients) were operated on before the gastrin radioimmunoassay was available. They include the patients first reported in 1955, as well as one patient operated on in 1948. Twenty-two of the patients had had approximately 50 previous gastric operations that were unsuccessful in controlling their gastric hypersecretion. The mean number of previous gastric operations was two, ranging from one to five.

The diagnosis of gastrinoma was confirmed by microscopic proof of tumor in 36 patients. In the remaining six patients, tumor was not found at operation, but all had elevated fasting gastrin levels and positive gastrin responses to secretin challenge.

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Diagnosis

Since 1971, the gastrin radioimmunoassay[2] and provocative tests with secretin and calcium gluceptate have made possible the earlier and more secure diagnosis of gastrinoma. The role of preoperative serum gastrin levels in predicting extent of tumor involvement, tumor aggressiveness, and patient survival is not clear. In general, the higher the fasting serum gastrin levels, the greater the likelihood of extensive tumor as well as tumor metastasis. While there were distinct exceptions, patients with localized or unidentifiable gastrinoma tended to have fasting serum gastrin concentrations below 1000 pg/ml that did not rise above 2000 pg/ml during calcium infusion. In contrast, patients with metastases had fasting serum gastrin concentrations above 1000 pg/ml and peak levels above 2000 pg/ml during calcium infusions. Lower preoperative levels correlated with improved five-year survival.

Way[3] has emphasized improved results with earlier diagnosis. Since 1971, we have encountered fewer patients who have had previous gastric operations or who have extensive tumor at surgical exploration. This has given rise to optimism about finding more localized, resectable, and potentially curable disease.

Gastrinomas are usually so small that they cannot be localized by CAT scans or ultrasound. Unfortunately, the gastrinoma within the pancreas is rarely visualized by angiography, but metastases to the liver may be demonstrated. Selective pancreatic vein sampling has been successful in localizing the anatomic area of pancreatic tumor involvement and has been found by Stadil, Passaro,[3,4] Mercadier[5] and others to be helpful. Gastroscopy may be considered in the search for a localized duodenal tumor, but positive findings are uncommon.

A total endocrine assessment is indicated, since the finding of one endocrine tumor suggests a search for others. Hyperparathyroidism in 25% of the patients in this series is consistent with other reports.[6] In patients with hypercalcemia and elevated parathyroid hormone levels, a subtotal parathyroidectomy should be the first surgical procedure. There is usually a decrease in the serum gastrin levels as the serum calcium levels fall following parathyroidectomy, but the fall is usually only temporary. Recurrent hypercalcemia has been observed in 33% of the patients with MEA or familial hyperparathyroidism.[7] In this series, six of seven patients had either persistent or recurrent hypercalcemia from ten months to six years after the initial operation performed elsewhere. Serum calcium levels should be measured at the time of gastrin determinations during long-term follow-up studies to detect recurrence.

Seventeen of the 42 patients with gastrinoma had a history of nephrolithiasis, suggesting the associated

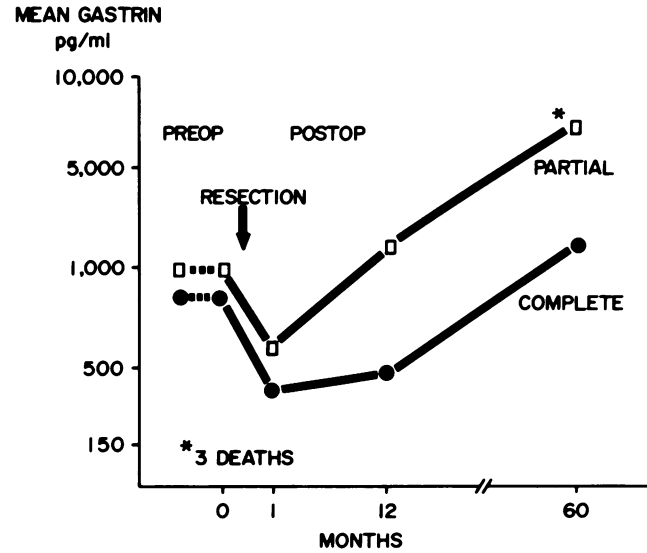

FIG. 1. Five-year gastrin trends following resection of gastrinoma.

diagnosis of hyperparathyroidism. However, in only ten of the 17 patients with nephrocalcinosis or calculi could the diagnosis of hyperparathyroidism be substantiated. Five of the remaining seven patients had had diarrhea or steatorrhea as a major symptom of a proved gastrin-producing tumor, and two had idiopathic kidney stones. The observation that in one-third of patients with kidney stones in this series, calculi were associated with enteritis and not with hyperparathyroidism opens the door to speculation as to the cause. This finding is consistent with the observations of others that kidney stones are more frequent in chronic diarrhea and steatorrhea.[8] Unfortunately, no calculi were available for chemical analysis or oxalate content. In addition, 12% of the patients had other endocrine tumors, including one adrenal cortical adenoma, one pituitary adenoma, and surprisingly, three pheochromocytomas.

Surgical Management

All 42 patients underwent surgical exploration to control the gastric hypersecretion as well as to aggressively search for and resect as much gross tumor as possible. An attempt to resect gastrinoma was made in 80% of the 36 patients in whom tumor was found. The operative mortality was 2.3%, the only death occurring in a patient who underwent emergency total gastrectomy for uncontrollable upper gastrointestinal hemorrhage one week following vagotomy and pyloroplasty.

Because all operations were performed before the advent of cimetidine, total gastrectomy was the only sure method to control the virulent ulcer diathesis in 80% of the patients (Table 1). Roux-en-Y reconstruction was routinely used. All accessible tumor was

TABLE 1. *Radical Surgery for Gastrinoma*

Procedure	Number of Patients
Total Gastrectomy &	34
Tumor Removal	26
hemipancreatectomy	19
total pancreatectomy	1
metastases	10
Tumor not removed	5
No tumor	3

resected from the pancreas, duodenum, lymph nodes, or liver in 61% of these patients.

A hemipancreatectomy was performed in 19 patients, over one-half of whom had total gastrectomy. In 13 patients, the procedure was performed to resect gross tumor, and in six as a blind resection in an effort to verify and excise microscopic tumor.

Metastatic gastrinoma was resected in 62% of the 16 patients with metastases having total gastrectomy. In three patients it was possible to remove all metastatic tumor; two patients had excision of large solitary lymph nodes, and one had a wedge resection of a solitary liver metastasis.

Despite the conviction in early days that total gastrectomy was essential as a life-saving procedure in most patients, eight patients did not have total gastrectomy (Table 2). In seven of these patients, tumor was so small that it could either be completely excised or was not found at the time of operation. These patients had less aggressive gastrinoma, and longer survival was anticipated.

Three of these patients did not have total gastrectomy because all accessible gastrinoma was successfully excised. The first patient, previously reported in 1956, was operated on in 1948. Following vagotomy and ligation of the left gastric artery, the gastric hypersecretion was reduced in volume by 50%, and the acidity was reduced from 129 to 59 mEq two weeks after vagotomy. Following removal of an islet cell tumor in the body of the pancreas, the volume decreased sharply to a total acidity of 7 mEq. This early patient clearly demonstrated the effectiveness of vagotomy in reducing gastric acidity in the presence of a noninsulin-producing islet cell tumor. The dramatic further fall in gastric acid values following removal of the tumor was consistent with an association between the tumor and the gastric hypersecretion. The patient died four years later with diffuse hepatic metastases, but she had relief from her gastric complaints for six months following the vagotomy and hemipancreatectomy.

The second had enucleation of a solitary pancreatic adenoma without a gastric procedure. This patient, alive and asymptomatic 14 years after operation, is one of only two of the entire group who has had long-term normal fasting and provocative serum gastrin concentrations. The third had excision of duodenal adenoma with vagotomy and pyloroplasty, and although asymptomatic, his gastrin levels have steadily increased.

An additional three patients had a vagotomy and less than total gastrectomy because of failure to identify tumor in the absence of an accurate gastrin radioimmunoassay. All have subsequently had elevated fasting gastrin levels, abnormal secretin bolus responses, and recurrent symptoms requiring cimetidine.

Of the remaining two patients, one underwent a series of five ulcer operations at other hospitals and at postmortem examination ten years after the initial operation was found to have a small gastrinoma within the duodenal stump. The eighth patient was presumed to have adenocarcinoma of the pancreas, and vagotomy and pyloroplasty along with cholecystoduodenostomy were performed. However, postoperatively this was proved on light microscopy to be an islet cell tumor, and elevated fasting serum gastrin concentrations were documented. The patient is presently living seven years after operation, and until cimetidine was available, she had had several massive gastrointestinal hemorrhages from multiple duodenal ulcerations.

Postoperative Follow-up Studies

The overall five-year survival rate in the 42 patients was 64%. The most important factor in the patients' long-term survival was the resectability and extent of the tumor. Regardless of the type of gastric operation, patients in whom all gross tumor was resected or in whom no tumor could be found after aggressive search had the best long-term survival rate (Table 3). Complete tumor excision was possible in over one half the patients with a five-year survival rate of 76%, compared to the five-year survival rate of 21% in the 14 patients whose gastrinoma was not completely resectable. Complete resection of tumor increased survival rates by an average of six years in those patients who died either as a result of or with extensive tumor ($p < 0.001$, unpaired t-test, $df = 14$, $t = 5.642$) (Table 4). Partial resection of metastatic tumor did not improve survival rates. Six of the 42 patients had no tumor

TABLE 2. *Lesser Surgical Procedures in Gastrinoma*

Procedure	Number of Patients
Vagotomy	7
gastroenterostomy	2
hemipancreatic	1
pyloroplasty	2
duodenal tumor	1
gastric resection	3
Enucleation of tumor	1

found at exploration, and all six are alive and have survived over five years.

Total gastrectomy performed in patients with the most extensive tumor resulted in five-year survival rate of 60%. Seven of the eight patients not having total gastrectomy, either because tumor could not be found or could be completely resected, survived five or more years. Prolonged survival could be anticipated in this group and was clearly related to the lesser extent of tumor. Seventy per cent of the patients who survived five years subsequently required cimetidine for relief of symptoms related to gastric hypersecretion, and were it not for this medication, all would have subsequently required total gastrectomy.

Modest decreases in fasting serum gastrin concentrations were noted in the immediate postoperative period in all of the patients having complete gross tumor excision and in one-half of those having partial resection. However, these changes were only transient, as gastrin concentrations five years after surgery had surpassed preoperative levels in the majority of patients (Fig. 1). Only two of the 42 patients have had persistently normal serum gastrin levels during a follow-up (as long as 14 years in one patient).

Approximately one-third of the patients have postoperative fasting gastrin levels below 500 pg/ml and tend to remain in this zone for five years or longer. However, over a five-year period, patients having fasting gastrin levels between 500 and 1000 pg/ml tend to show an upward trend. The aggressiveness of the tumor is illustrated by the decrease from 28% below 1000 pg/ml to only 6% below 1000 pg/ml over a five-year period. The three deaths during the past five years occurred in patients with gastrin levels above 1000 pg/ml. The percentage of patients in this group increased from 44% in 1975 to 62% in 1980.

Quantitation of the individual molecular species of gastrin may improve detection of tumor spread. Fabri et al.[10] evaluated 17 of these patients having total gastrectomy and proved tumor and found that of the ten patients with known metastases, seven had levels of G-17 greater than 20% of total gastrin, whereas only one patient of seven with no gross metastasis had a G-17 value greater than 20% of total gastrin. Trends in the postoperative gastrin levels apparently do indicate impending disaster, and it may be that chemotherapy should be considered when the postoperative fasting gastrin level exceeds 1000 pg/ml and the provocative infusion studies exceed 2000 pg/ml.

TABLE 3. *Control of Tumor in Gastrinoma (Procedure vs. Five-year Survival Rate)*

Procedure	Number of Patients	Per Cent
No tumor found	6	100
Complete resection	22	76
No resection	7	30
Partial resection	7	14

TABLE 4. *Complete Tumor Resection Significantly Increased Survival*

Tumor Resection	Number of Patients	Average Survival Rate (Years)*	Tumor Death (No.)	Average Survival Rate (Years)†
Complete	22	9	5	7.75
Not possible	14	3	8	2.5

* $p < 0.01$ unpaired t-test, $t = 3.140$, $df = 34$.
† $p < 0.001$ unpaired t-test, $t = 5.682$, $df = 12$.

It is difficult to evaluate the benefits of chemotherapy in these unusual tumors with a bizarre and unpredictable growth pattern. Experience with five patients was described in 1976,[11] and chemotherapy has not been repeated in the last four years. As anticipated from clinical evaluation, two patients died of extensive metastatic disease one and three years after the last treatment. The clinical impression was that the quality and duration of both patients' lives had been improved by chemotherapy. The other three patients are living, but whether they would still be living had they not had chemotherapy is unknown. More recently, chlorozotocin 200 mg/m^2 as a bolus every six weeks has been recommended.[12] This is reserved for good-risk patients with proved tumor, significant symptoms, and disease measured with gastrin levels. Patients should not have received prior radiation, and at least three weeks must intervene between operation and chemotherapy.

Discussion

The introduction of the H_2 receptor antagonist, cimetidine, has revolutionized the therapy of gastrinoma. The so-called "chemical gastrectomy" has gradually replaced surgical total gastrectomy in the majority of patients. However, cimetidine, as did total gastrectomy, only treats the potentially life-threatening manifestations of gastrinoma and does not alter potentially fatal progressive tumor growth. Surgery should now be directed toward control of the tumor rather than the complete eradication of the massive gastric hypersecretion by total gastrectomy.

Eleven authorities in the management of gastrinoma were asked their opinions.[13] There was general agreement as to the value of cimetidine in the preoperative and postoperative control of gastric hypersecretion. But, total gastrectomy continued to be the treatment of choice when cimetidine failed, and several elected this procedure routinely, especially if the symptoms

TABLE 5. *Recommended Therapy for Gastrinoma*

Therapy	Operation		Follow-up
Cimetidine			
Parathyroidectomy?			
Surgical exploration			
negative	V & P		Cimetidine
tumor	V & P	Resect	Cimetidine
metastasis	V & P	Resect	Cimetidine
			Chemotherapy?

were severe and metastases were present. One favored total gastrectomy in children. All agreed that a search for solitary tumors was indicated. Resection of tumor was uniformly recommended, while one did not favor partial tumor resection. Despite various reports of undesirable side effects from cimetidine,[14,15] no mention was made of side effects other than gynecomastia in 4% of patients. The more experienced the surgeons in gastric and pancreatic surgery, the more aggressive was their approach.

Cimetidine usually provides immediate relief of symptoms and should be prescribed as soon as the diagnosis is confirmed by secretin challenge. The drug prevents the catastrophic complications formerly seen while the patient's operative risk is improved and a complete endocrine survey is made. If the patient is hypercalcemic with elevated serum parathormone levels, a subtotal parathyroidectomy should be the initial operation.

Regardless of the ability of cimetidine to control the patient's symptoms, all patients should be explored. The fear of exploratory laparotomy must not lead to reliance on long-term medication to provide symptomatic relief; such a practice will foster further growth of potentially resectable tumor. Twenty-five years' experience in the treatment of gastrinoma has emphasized that the most important factor in long-term survival rate is the ability to detect and resect all accessible tumor. Aggressive exploration identified gastrinoma in three-fourths of the patients, and it was completely resected in 61% of the patients. Complete resection of tumor extended a patient's life by an average of six years and resulted in a 76% five-year survival rate (Tables 3 and 4). Therefore, surgical exploration to search out and resect all accessible tumor is of primary importance in the treatment of gastrinoma.

The extent of the surgical procedure on the pancreas should be governed by the expertise of the surgeon in this anatomic area. Some prefer a Whipple procedure for tumors in the head of the pancreas or duodenum.[16] Total pancreatectomy should be avoided because of the possibility of total gastrectomy later. Lymph nodes adjacent to the pancreas should be excised to establish the presence of metastases and in the hope of improving survival. Large obviously tumor-laden lymph nodes should also be excised, and solitary metastases to the liver removed by wedge resection.

At exploration, in addition to resection of gastrinoma, cimetidine control may be facilitated by performing a vagotomy, which has been shown to reduce gastric acid production by 50% in the presence of gastrinoma. Others have speculated on the enhancing effect of vagotomy on cimetidine therapy.[17] Pyloroplasty should probably be performed to facilitate the detection of a duodenal submucosal adenoma.

If tumor is not found at exploration, the effort has not been wasted, as a reliable prognosis for long-term survival can be given to the patient and the family, and vagotomy performed to improve the ability of cimetidine to control the patient's symptoms.

Postoperative evaluation indicates that hypergastrinemia will persist in the majority of patients after tumor resection over a period of five years (Fig. 1). Less than 5% of the patients had persistently normal fasting gastrin concentrations after operation. Thus, if the patient is explored and tumor resected, cimetidine must be continued for the patient's lifetime, unless total gastrectomy has been performed.

Total gastrectomy is reserved for patients who have failed on cimetidine therapy, either because of lack of compliance with the medication regimen, drug tolerance, or progressive gastric hypersecretion. Regression of tumor, especially with metastasis to the liver, has been reported by Friesen[18] and others[19] following total gastrectomy, but the occurrence is not sufficiently frequent to warrant the continuation of routine total gastrectomy for this reason. Some have suggested total gastrectomy be considered in young patients because of the previously reported good results and the anticipated long survival rate.[20] But currently, the need for such a radical approach in even a young patient must be questioned if tumor can be resected and gastric hypersecretion controlled by vagotomy and cimetidine.

The role of chemotherapy in the management of metastatic gastrinoma is uncertain. It is difficult to predict which patients will derive benefit from this treatment. Chemotherapy with either streptozotocin or chlorozotocin may be considered in a few patients with aggressive or extensive tumor indicated by fasting gastrin levels above 1000 pg/ml, peak gastrin levels above 2000 pg/ml during calcium infusion, and a G-17 greater than 20% of fasting gastrin.

The demonstrated increase in survival in this series justifies aggressive resection of gastrinoma, whether it be in the pancreas, duodenum, lymph nodes, or liver. The surgeon's role has changed from performing routine total gastrectomy to performing vagotomy and pyloroplasty in addition to excising all accessible tumor (Table 5).

Summary

Cimetidine, the so-called "chemical gastrectomy," has gradually replaced surgical total gastrectomy to control the virulent gastric hypersecretion in the majority of patients with gastrinoma. However, like total gastrectomy, cimetidine treats only the consequences of gastrinoma, and its use will not alter progressive tumor growth which is the most frequent cause of death in these patients. During the past 25 years, we have treated 42 patients with gastrinoma and have found that a direct and aggressive surgical approach to the tumor improves long-term survival rate.

Surgical exploration identified gastrinoma in nearly three-fourths of patients, and resection of tumor was clearly of benefit. The five-year survival rate was 76% in patients having complete resection of all gross tumor from the pancreas, duodenum, lymph nodes, or liver, in comparison to 21% in those in whom complete tumor resection was not possible. When all identified tumor was excised, the duration of survival increased by an average of six years. In six patients, no tumor was identified and all six are alive, surviving at least five years.

As long as the patient's symptoms can be controlled with cimetidine, total gastrectomy is no longer required. However, surgical exploration is advised routinely, in order to search out and resect the gastrinoma completely and improve the patient's long-term survival. With earlier diagnosis afforded by the gastrin radioimmunoassay, it can be expected that more patients will have resectable tumor. Vagotomy may facilitate postoperative cimetidine therapy, as it may reduce gastric acid production. Importantly, if tumor is not found, a hopeful prognosis for prolonged survival may be given the patient and the family. Even after complete excision of gross tumor, only 5% of patients will have persistently normal serum gastrin levels and be asymptomatic, the remaining 95% will require lifetime cimetidine therapy. Total gastrectomy is reserved for patients who either fail with cimetidine therapy or cannot comply with the medication schedule, or who do not wish to take cimetidine for the rest of their lives.

The surgical skill, judgment, and experience previously required to perform total gastrectomy can now be well spent in a more aggressive search for and resection of the gastrinoma. A diagnosis of gastrinoma is an indication for early surgical exploration by a surgeon with expertise in both pancreatic and gastric procedures.

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Discussion

Professor Richard B. Welbourn (London, England): It has been a rare treat today to hear from Dr. Zollinger and from Dr. Ellison, Jr., this 25-year review of the growth of his and Dr. Ellison, Sr.'s original idea and to learn of their impressive results.

My own experience is not nearly so great, but I treated my first patient with a gastrinoma in 1957. I will not quote any statistics, but will highlight some of the lessons which we have learned and problems which we have encountered.

Benign resectable gastrinomas are undoubtedly rare, but I see regularly a patient whom I inherited from a retired colleague, Mr. Leslie Lauste. In 1961 Lauste found and removed two benign tumors from the head of the pancreas during the fourth operation (not total gastrectomy) for aggressive ulcer disease. The patient did well and 19 years later has a normal plasma gastrin level.