The Early Diagnosis of Gastrinoma

IRVIN M. MODLIN, M.D., BERNARD M. JAFFE, M.D., ANTHONY SANK, M.D., DEBORAH ALBERT, M.D.

Despite the increasing awareness of gastrinoma and its lethal peptic ulcer sequelae, the diagnosis is often initially missed or made as a terminal event. The authors screened all patients with peptic ulcer symptoms serious enough to warrant hospital admission or those associated with diarrhea, nephrolithiasis, hypercalcemia, or pituitary abnormality. In a one-year period (1979–1980) nine (of 14 suspected) new gastrinoma patients were identified using a sensitive and specific gastrin radioimmunoassay in combination with provocative tests including IV secretin, calcium, and food. Conventional upper GI series, CAT scan, arteriography, and endoscopy provided no additional information other than to confirm the presence of ulcer disease. Basal plasma gastrin levels were more than 200 pmol L^{-1} in only three of the nine (normal fasting plasma gastrin levels are less than 25 pmol L^{-1}). Three patients presented with acute ulcer perforation, and the diagnosis of gastrinoma was suspected because of multiple ulcers and pancreatic masses. In three other patients, previous duodenal ulcer surgery had failed. One patient with dyspepsia, high basal plasma gastrin, negative secretin and calcium infusion studies, and a positive meal test was diagnosed as having G-cell hyperplasia; this was confirmed by biopsy and antral gastrin extraction. Antrectomy alone resulted in cure. In all patients tested, a positive calcium infusion or secretin bolus (greater than 100% rise over basal) strongly suggested the diagnosis of gastrinoma, which was confirmed at surgery. In the acute perforations, initial management with omental patch and cimetidine therapy allowed survival of two patients, while emergency total gastrectomy in the third resulted in death due to esophagojejunal leak. Elective patients were treated with cimetidine initially for at least two weeks before total gastrectomy. In this group there were no operative mortalities, and postoperative morbidity was minimal. This series illustrates three important points: (1) careful screening of an ulcer population using gastrin radioimmunoassay and provocative tests has enabled a high yield of gastrinomas while conventional investigations are of minimal value; (2) a high index of suspicion in appropriate cases is necessary; and (3) total gastrectomy performed under elective circumstances is safe and allows the patients to resume a normal and healthy life without the sequelae of aggressive peptic ulceration or daily drug administration.

From the Department of Surgery, Downstate Medical Center, Brooklyn, New York

THERE HAS BEEN a considerable evolution in the management of gastrinomas since the original description of the Zollinger–Ellison syndrome in 1955.[1,2] Whereas the original concept had been to remove the pancreas and the stomach, more current views suggest that total gastrectomy alone is more effective.[3–5] More conservative opinions, based on marginal evidence, have advocated lesser procedures such as truncal or parietal cell vagotomy.[6,7] The use of long-term maintenance cimetidine has also received serious consideration, although insufficient data are available at present to define which patients will be most amenable to this therapy.[8]

Although early reports in the literature all described cases of fulminant ulcer diatheses and associated major sequelae, it has become apparent in recent times that the clinical manifestations of gastrinoma may be quite subtle.[5,9] The reason for this may well be a purely temporal phenomenon, although experience suggests that some gastrinomas are *de facto* less aggressive in their clinical course. It has been suggested that plasma gastrin levels or the percentage of specific circulating components may be of use in the prediction of the severity of the disease.[10]

It was felt that it would be of some clinical relevance and considerable interest to evaluate patients with peptic ulcer symptomatology in an effort to find patients early in the course of this syndrome. Since the authors had recently established a gastrin radioimmunoassay research laboratory in a geographic area that had previously not had this facility, the opportunity to screen a virgin population was ideal.

This report outlines the authors' experience in the early diagnosis of gastrinoma in a general urban population over the course of a one-year period (1979–1980). It emphasizes that by the employment of appropriate clinical criteria and the availability of an accurate and sensitive radioimmunoassay, impressive numbers of Zollinger–Ellison patients may be detected in a standard population group. Further, it suggests that the time

Supported in part by USPHS Grant 5-RO1 AM26522-02 from the N.I.A.M.D.D. and by the Foundation for Surgical Education and Investigation.

Reprint requests: Irvin M. Modlin, M.D., Department of Surgery, Box 40, Downstate Medical Center, 450 Clarkson Avenue, Brooklyn, New York 11203.

Submitted for publication December 16, 1981.

0003-4932/82/1100/0512 $01.10 © J. B. Lippincott Company

course of this disease often may be delayed and that with a high index of suspicion early cases can be detected and treated before the catastrophic sequelae of the fulminant disease are apparent. The relatively short postoperative follow-up period supports the contention that in patients with a gastrinoma a total gastrectomy is a safe and extremely well-tolerated procedure that allows a survival period not characterized by the severe weight loss and unpleasant digestive sequelae that often are associated with similar treatment for carcinoma of the stomach.

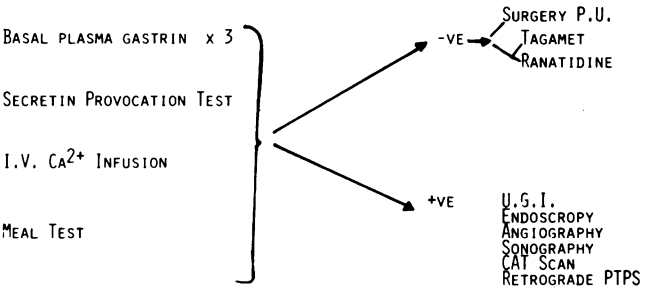

FIG. 1. If basal gastrin levels were elevated (>25 fmol ml^{-1}), provocative tests (secretin, calcium meal) were undertaken followed by topographical investigation and the appropriate treatment.

Methods

A number of criteria were used to select patients who were to be screened. All patients with a peptic ulcer complication or symptomatology serious enough to warrant admission to Downstate Medical Center and its affiliated hospitals were included in this study. Recurrence of peptic ulcer or the association of diarrhea, hypercalcemia, nephrolithiasis, pituitary abnormalities, or gastric hypersecretion were also used as criteria. Over a one-year period, 48 patients who fell into one of more of these categories were studied.

Each individual had fasting plasma drawn on three separate occasions for basal gastrin estimation. The upper limit of normal in the gastrin assay is 25 pmol L^{-1}. Using this as a cut-off point, the authors were able to identify 14 patients with basal hypergastrinemia. A protocol study including secretin, meal, and calcium provocation tests was then undertaken in sequential order on separate days with at least 24 hours between each test. Patients were fasted for 12 hours before each study (Fig. 1).

The method of the secretin provocation study was as follows: secretin, 2U/Kg (Karolinska GIH), was administered as an IV bolus and blood drawn at one, three, five, ten, 20, and 30 minutes from an indwelling venous catheter. The secretin test was considered positive if the peak gastrin levels attained were 100% over basal values or increased by more than 50 pmol L^{-1} (Fig. 2).

A calcium infusion study was undertaken as the second test. Calcium gluconate (4 mg Ca $Kg^{-1}hr^{-1}$) was infused continuously IV over three hours, and peripheral venous blood sampled at 15-minute intervals. The calcium test was interpreted as positive if the peak gastrin levels were 100% increased over basal (Fig. 3).

The meal provocation consisted of a standard test meal (carbohydrate 65 gm; protein 20 gm; fat 28 gm) ingested over ten minutes. Blood was drawn at ten-minute intervals over a two-hour period. In the authors' experience a gastrin increment of at least 50 pmol/L represents a normal meal response (Fig. 4).

All plasma samples were stored at −20 C until assayed for gastrin. The gastrin radioimmunoassay utilized in this laboratory uses a C-terminal gastrin specific antibody that recognizes all molecular forms of gastrin on an equimolar basis. The ID 50 for the assay is 1.5 pmol L^{-1}, and there is no cross reactivity with any other known peptide. Results are expressed in terms of a standard of pure natural human nonsulfated little gastrin (HG17-1) in pmol L^{-1}. Exact details of this assay have been published elsewhere.[11] All provocative test samples were measured in duplicate in one assay to avoid interassay variation.

Once a patient had been biochemically diagnosed as having a gastrinoma on the basis of the provocation tests, topographic localization studies were undertaken. These included upper gastrointestinal radiology, selective pancreatic angiography, computer assisted tomographic scanning, and endoscopy. Thereafter, the deci-

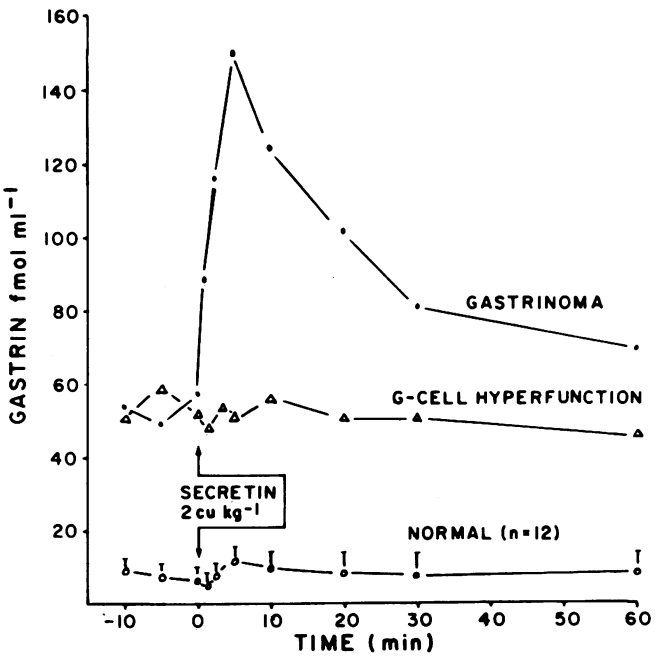

FIG. 2. The secretin provocation test indicated an insignificant plasma gastrin response in 12 normal controls and no alteration in the basal hypergastrinemia of G-cell hyperfunction. In a gastrinoma patient a significant elevation of plasma gastrin was evident.

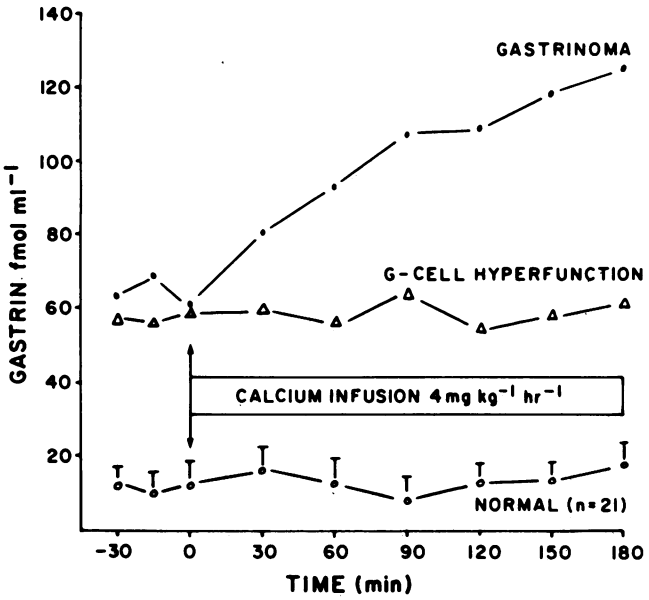

FIG. 3. Calcium infusion released no gastrin in 12 normal controls and did not alter the basal hypergastrinemia of the G-cell hyperfunction patient. In a gastrinoma patient a sustained steady increase of plasma gastrin occurred throughout the course of the calcium infusion.

sion was made as to whether the condition should be surgically managed. In those patients with a diagnosis of gastrinoma, surgical treatment was preceded by at least two weeks treatment with cimetidine to facilitate the operative management of the peptic ulcer. All patients underwent a transabdominal total gastrectomy with Roux-en-Y anastomosis, except one who underwent an antrectomy for antral G-cell hyperplasia.

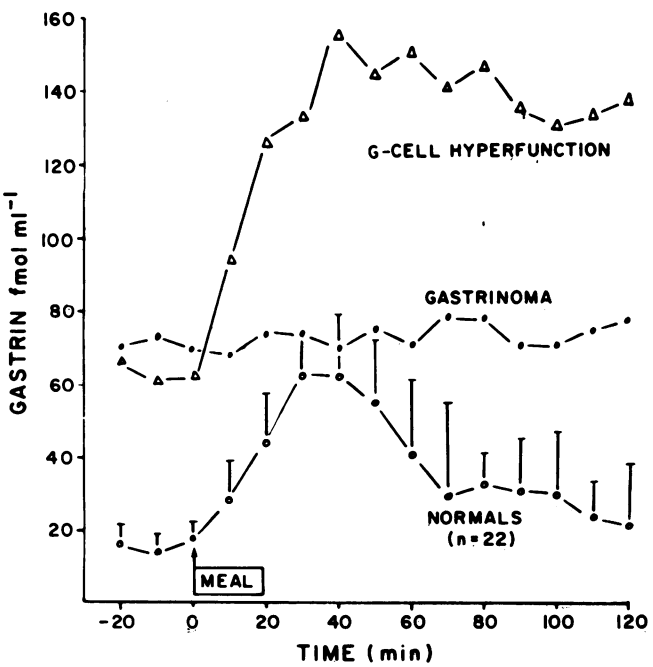

FIG. 4. The meal provocation test resulted in a significant increase of plasma gastrin in normal controls while the basal hypergastrinemia of a gastrinoma was not altered. The plasma gastrin response of the patient with G-cell hyperfunction was markedly accentuated.

Results

Of 48 patients initially screened, only 14 were found to have basal hypergastrinemia. Fasting plasma gastrin in these patients ranged from 60 pmol L^{-1} to 742 pmol L^{-1}. Of this group four patients were found to have a normal gastrin meal response and no response to IV secretin or calcium challenge. The authors interpreted these data to exclude the diagnosis of gastrinoma in these four individuals. Careful investigation revealed no cause for this nonstimulatable basal hypergastrinemia (range 78–118 pmol L^{-1}; mean 76 ± 14 pmol L^{-1}). Only eight gastrinoma patients were fully tested since one died during emergency operation. Six of the eight had a positive secretin test and five, a positive calcium provocation study. In all the gastrinoma patients tested, meal provocation studies were normal (Fig. 5).

L.N. had basal hypergastrinemia (62 ± 11 pmol L^{-1}) but did not respond to secretin or calcium. Meal provocation, however, was markedly abnormal and an endoscopic antral biopsy revealed a significantly elevated level of immunoreactive antral gastrin (normal: 2204 ± 231 pmol gm^{-1}; LN: 14,302 pmol gm^{-1}) (Fig. 6).

Eight of the gastrinoma patients were male, and seven were less than 35 years of age. Three had previous peptic ulcer surgery, and six presented with complications of peptic ulcer disease. Two patients presented with diarrhea as their chief complaint in addition to dyspepsia, and two patients had hypercalcemia due to parathyroid disease and were identified as multiple endocrine neoplasia type 1 kindred. LN was identified as a patient with a G-cell hyperplasia and underwent antrectomy (Bilroth 1 anastomosis without vagotomy); she has since been free of dyspepsia. All of the nine patients with Zollinger–Ellison syndrome underwent a total gastrectomy. One (PM) had an acute perforation and hemorrhage necessitating emergency operation at which time a total gastrectomy was undertaken. He died four days later from complications related to a leak of the esophagojejunal anastomosis. The eight patients who were electively operated upon each received at least two weeks cimetidine therapy (400 mg g.i.d.) and thereupon underwent total gastrectomy with Roux-en-Y anastomosis. All had overt pancreatic masses, and four had evidence of diffuse metastatic disease throughout the liver and peritoneal cavity. No pancreatic biopsy was undertaken at surgery since in the authors' experience this has only added to the morbidity and has provided no additional information. In the series of eight elective total gastrectomies, there were no deaths, but one patient had an esophagojejunal anastomotic leak that rapidly sealed and did not delay oral alimentation. He subsequently developed mild stenosis that resolved with one dilation. At most recent follow-up, all eight are in good health,

eating a normal diet, and none have significant postprandial symptomatology. Five of the eight patients have increased their preoperative weight by greater than 10%, and only one man (ET) with documented metastases has suffered significant weight loss.

Discussion

Almost 350,000 patients with the primary diagnosis of peptic ulcer were hospitalized in the U.S. in 1977. Of these, 140,000 had operations, about 19,000 had perforations, about 100,000 had bleeding, and in total, almost 6,000 died.[12] It is thus evident that the morbidity and mortality of peptic ulcer disease are not insignificant. Accurate information as to the exact incidence of gastrinoma patients in the general population is not available, although Rehfeld has estimated the incidence at one patient per year per million of the population.[13]

This report documents the authors' experience over a one-year period at a University Medical Center that previously had no special interest or ability to screen patients with gastrointestinal complaints to diagnose the Zollinger–Ellison syndrome. We would emphasize that a high index of suspicion coupled with the availability of facilties to investigate these patients is mandatory to establish the diagnosis. For this reason, the authors developed a set of criteria that has enabled clinicians not entirely familiar with the manifestations of gastrinoma to be aware of the different settings in which such patients might present.

Seven of the patients were less than 35 years of age and had symptoms for less than two years, a far shorter history and younger age group than generally reported. This finding would support previous suggestions that many of these tumors are slow growing and have been present for some time before diagnosis.[5] The data of the Z–E tumor registry described a symptomatic period of greater than five years in 20% of patients.[14,15] Although early diagnosis and total gastrectomy have not clearly been shown to affect tumor growth, there is little doubt that it will prevent the fateful sequelae of acute ulcer complications.[16,17,18] The follow-up period is not long enough to derive a firm conclusion regarding long-term survival based on early operation. However, it is the authors' current experience that these patients have done far better without the pain, bleeding, and malabsorptive sequelae of their acid hypersecretion. A recent report by Thompson further supports this observation.[5]

Since there are a number of different causes of hypergastrinemia, it is important to have access to a sensitive and specific gastrin radioimmunoassay. The measurement of gastric acid secretion is useful but sometimes difficult to evaluate accurately in patients with previous gastric surgery.[19] Early diagnosis of the Zollinger–Ellison syndrome may fail if assay sensitivity is low, and a number of cases with only marginally elevated basal values of plasma gastrin may be ignored if appropriate provocative testing is not available.[20] The secretin test is particularly useful, since it is sensitive and specific, assuming pure secretin (Karolinska-GIH) is used. In addition, it is comfortable for the patient and can be completed within 45 minutes.[20,21] Other authors have also supported the continued use of secretin in the diagnosis of gastrinoma, although a number of false negatives have been reported.[3] Whether this represents the use of inactive secretin or identifies a subgroup of nonstimulatable gastrinomas has not been clearly resolved. The calcium infusion test appears to be almost as reliable but takes far longer, and the patients often have some

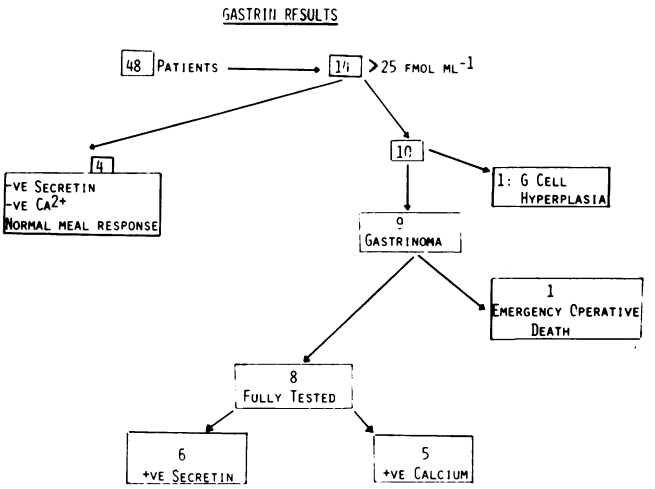

FIG. 5. The measurement and assessment of plasma gastrin levels in the 48 patients who met the criteria for investigation. Four had basal hypergastrinemia of unexplained origin, since both calcium and secretin tests were negative and the meal response was within normal limits. One patient died after emergency surgery and was not fully tested.

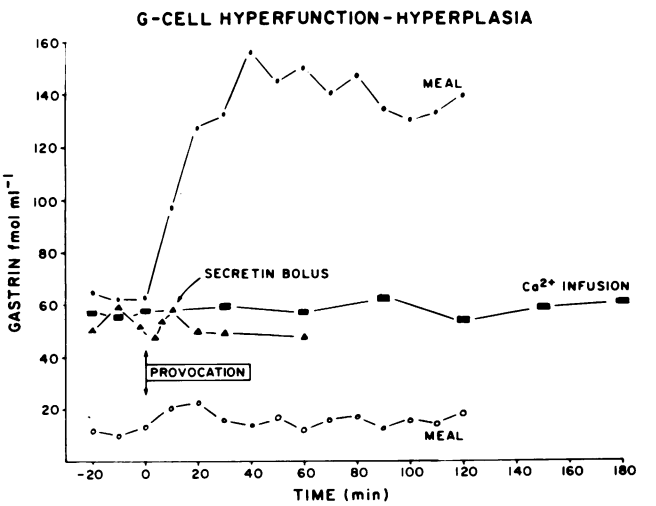

FIG. 6. The G-cell hyperplasia patient exhibited a negative secretin test (▲ – ▲) and a negative calcium infusion test (■ – ■). The preoperative meal response (● – ●) was markedly accentuated. After operation (○ – ○) the basal gastrin level was significantly reduced, and there was only a marginal gastrin response to a test meal.

discomfort in the form of parasthesiae and twitching during the study. However, the major advantage is that calcium gluconate is far cheaper and more readily available than secretin.[21] The meal test is useful, since it is easily carried out and provides useful supportive data in addition to the calcium and secretin studies. Our Z–E patients did not have significant meal-induced release of gastrin. This probably reflects either the nature of autonomous peptide secretion by the tumor or suggests that luminal stimulatory mechanisms for gastrin release are either nonfunctional or at maximum capacity in this condition. The meal test is, however, useful in establishing the cause of hypergastrinemia in the rare condition of antral G-cell hyperfunction. In this poorly understood situation, hypergastrinemia is apparently related to massive over-production of gastrin by the antrum. The meal-stimulated gastrin release is enormously exaggerated, yet both the secretin and calcium tests are negative. The pathogenesis of this clinical entity is not clearly understood but immunofluorescent histochemistry and gastrin extraction have reported both increased gastrin concentrations and elevated number of gastrin-containing cells in the antrum.[22] Simple antrectomy has been reported to be sufficient in the management of such patients and resulted in rapid amelioration of the symptoms; furthermore, postoperative basal plasma gastrin levels returned to normal, and there was no plasma gastrin response to ingested food.

All the patients with basal hypergastrinemia were intensively studied. This process enabled the authors to detect nine gastrinomas in 48 tested patients over a period of one year. At this time, it may not prove to be either cost- or time-effective to undertake testing of all patients with upper gastrointestinal symptoms. It is probable, however, that there is a period in the genesis of this disease that basal gastrin levels may be normal, yet stimulation with calcium or secretin might unmask a tumor. The identification of patients at this stage of the disease process represents an unresolved problem.

Once tumors were functionally diagnosed, a number of topographical studies were utilized in an attempt to formally localize them. Upper gastrointestinal radiology, ultrasonography, and endoscopic retrograde cholangiography (two patients) provided no further information. Selective pancreatic angiography identified tumors in three patients, all of whom had late stage disease with hepatic metastases. Computerized axial tomography did not clearly delineate the gastrinoma except in the three patients with advanced disease. The authors performed percutaneous transhepatic portal venous sampling in three patients but did not derive any further information than was already available by angiography and CAT scan. This method has, however, been reported to be of considerable use in the identification of multiple or covert tumors and, thus, facilitate appropriate surgical resection.[19]

The subject of the ideal surgical management of gastrinoma is controversial and revolves around the question of whether pancreatectomy might remove the tumor completely or whether eradication of the disease is impossible and surgery should be directed at alleviating the consequences of acid overproduction. In a significant percentage of patients the tumor may not be identifiable either by investigation or at operation. Under such circumstances a blind pancreatectomy would be a dubious method of potentially removing a gastrin-producing lesion. Furthermore, in over 50% of the patients with an identifiable tumor, further tumors are often covert both to the eye or the exploring hand because of the multicentric or metastatic nature of the disease within the pancreas. Since at least 60% of gastrinomas are malignant and more than half have hepatic metastases at the time of diagnosis, the advantages of pancreatic resection appear marginal. The combination of a failed pancreatic resection followed by a total gastrectomy has been reported by Fox and colleagues to result in disastrous nutritional consequences.[15] In a detailed analysis of the 800 patients in the ZES tumor registry, those with tumors in the head and body of the gland treated with pancreatectomy or pancreaticoduodenectomy did extremely poorly because of either multiplicity of tumors, recurrence of the disease, or the high perioperative mortality. Although it has been argued that single lesions of the tail of the pancreas might be best treated by surgical excision, experience had indicated that this is rarely the case. Isolated reports of successful excision of duodenal wall tumors exist, but the incidence of solitary lesions in the duodenum is low since many of these patients have multicentric concomitant pancreatic lesions. Thus, true cure resulting from tumor excision is theoretically impossible in at least 80% of patients.[6] However, isolated reports of the removal of solitary pancreatic benign gastrinomas with long-term cure do exist. In general, the main thrust of treatment in all cases should be aimed at preventing the complications of the disease process. An analysis of 571 gastrinoma patients showed that 70% of them survived five years after total gastrectomy. Conversely, only 42% who had anything less than a total gastrectomy survived five years.[15] Although total gastrectomy does not prevent tumor growth or delay metastatic spread, the reduction in ulcer complications and their related morbidity and mortality provides more than sufficient rationale for advocating this procedure. In an analysis of 296 deaths of patients with gastrinomas, 37% were caused by ulcer problems and 26% caused by postoperative complications. Thus, removal of all acid-secreting mucosa abolishes the ulcer-related deaths and in experienced hands under appropriate conditions, the mortality for elective total gastrectomy at this time should not be more than 2% to 3%.

Long-term medication or palliative procedures such

as vagotomy have their proponents, but no substantial data has yet emerged to enable a firm decision to be made to change the definitive treatment. It is evident from this study that total gastrectomy is a safe procedure in patients with gastrinoma. The addition of an appropriate length Roux-en-Y anastomosis avoids the sequelae of reflux biliary esophagitis and results in minimal postoperative problems. Many of these tumors, although metastatic, are slow growing and the patients do not have the rapid downhill course so often associated with total gastrectomy for carcinoma of the stomach. Thus, the unfavorable nutritional sequelae so often identified with total gastrectomy do not appear to apply to patients with gastrinoma who undergo total gastrectomy. Previous adverse reports of the effect of total gastrectomy[23] presumably reflect a comparison of two different disease processes and have been inappropriately used to cast aspersions upon this procedure as the operation of choice in patients with gastrinoma.

One patient who underwent total gastrectomy as an emergency procedure developed a major anastomotic leak and perished. This experience further reinforces the authors' conviction that at least two weeks preoperative therapy with cimetidine is necessary to reduce inflammation and edema, thereby facilitating ideal resection and anastomosis. If emergency surgery for bleeding or perforation is unavoidable, the safest and most expeditious procedure should be undertaken, usually total gastrectomy with catheter duodenostomy and esophageal closure with proximal intubation. In addition, the patient should be placed on intravenous hyperalimentation. In the authors' experience including one patient in this series, lesser surgical procedures have failed to protect the gastrinoma patient from further complications. Only when the patient is stabilized and the physical condition optimal should elective esophagojejunostomy be undertaken.

The authors have briefly detailed their experience in the identification of gastrinoma tumors from a standard group of patients with gastrointestinal disease. The use of appropriate screening criteria and a formal protocol for the evaluation of hypergastrinemia has permitted the diagnosis and management of a number of patients prior to the onset of the catastrophic consequences of the long-term unrecognized disease process. The development of sophisticated and sensitive radioimmunoassays for gastrin has further allowed the authors to differentiate normal patients from those with hypergastrinemia of tumor and nontumor origin. Screening criteria has been adapted to enable careful investigation of individuals who might be harboring this specific ulcer diathesis. Total gastrectomy has proved to be a safe and reliable method of treatment when undertaken electively; it is extremely well tolerated by patients suffering from the Zollinger–Ellison syndrome. Emphasis on the early identification of patients with gastrinoma at this time provides the most reasonable basis for ideal long-term management and survival.

References

1. Deveney CW, Deveney KS, Way LW. The Zollinger–Ellison syndrome 23 years later. Ann Surg 1978; 188:384–393.
2. Zollinger RM, Ellison EC, Fabri PJ, et al. Primary peptic ulcerations of the jejunum associated with islet cell tumors. Ann Surg 1980; 192(4):422–430.
3. Stage JG, Stadil F. The clinical diagnosis of the Zollinger–Ellison syndrome. Scan J Gastroenterol 1979; 14(Suppl 53):79–91.
4. Stage JG, Stadil F, Fischerman K. New aspects in the treatment of Zollinger–Ellison syndrome. In: Creutzfeld W, ed. Cimetidine. (Int. Congress Series No. 443) Amsterdam: Excerpta Medica, 1978; 137–48.
5. Thompson J. The Zollinger–Ellison syndrome. Contemporary surgery. 1979; 14:77–122.
6. McCarthy DM. The place of surgery in the Zollinger–Ellison syndrome. N Engl J Med 1980; 302(24):1344–1347.
7. Richardson CT, Feldman M, McClelland RN, et al. Effect of vagotomy in Zollinger–Ellison syndrome. Gastroenterology 1979; 77:682–686.
8. Lamers CBH, Van Tongeren JHM. Comparative study of the value of the calcium, secretin and meal stimulated increase in serum gastrin to the diagnosis of the Zollinger–Ellison syndrome. Gut 1977; 18:128–135.
9. Modlin IM. Endocrine tumors of the pancreas. Surg Gynecol Obstet 1979; 149:751–769.
10. Fabri PJ, Johnson JA, Ellison CE. Prediction of progressive disease in Zollinger–Ellison syndrome—comparison of available preoperative tests. J Surg Res 1981; 31:93–97.
11. Jaffe BM, Walsh JH. Gastrin and related peptides. In: Jaffe B, Behrman H, eds. Methods of Hormone Radioimmunoassay. New York: Academic Press, 1979; 455–477.
12. Grossman MI. Epidemiology and pathogenesis of peptic ulcer. Practical Gastroentrol. 1979; 3:9–13.
13. Rehfeld JF. Radioimmunoassay in the diagnosis, localization and treatment of endocrine tumors in gut and pancreas. Scan J Gastroenterol 1979; 14(Suppl 53): 33–38.
14. Fox PS, Hoffman JW, Wilson SD, DeCosse JJ. Surgical management of the Zollinger–Ellison syndrome. Surg Clin North Am 1974; 54:395–407.
15. Fox PS, Hoffman JW, DeCosse JC, Wilson SC. The influence of total gastrectomy on survival in malignant Zollinger–Ellison tumors. Ann Surg 1974; 180:558–556.
16. Davis CE Jr, Vansant JH. Zollinger–Ellison syndrome. Spontaneous regression of advanced intra-abdominal metastases with 20-year survival. Ann Surg 1979; 189:620–626.
17. Freisen, SR. Editorial on the ulcerogenic syndrome. In: Friesen SR, ed. Surgical Endocrinology: Clinical Syndromes. Philadelphia: JB Lippincott, 1978; 211–214.
18. Freisen SR. Effect of total gastrectomy on the Zollinger–Ellison syndrome: observation by second look procedure. Surgery 1967; 62:609–613.
19. Ingemassen S, Larsson LI, Lunderquist A, Stadil F. Pancreatic vein catheterization with gastrin assay in normal patients and in patients with the Zollinger–Ellison syndrome. Am J Surg 1977; 134:558–563.
20. Isenberg J, Walsh JH, Passaro E, et al. Unusual effect of secretin on serum gastrin, serum calcium and gastric acid secretion in a patient with suspected Zollinger–Ellison syndrome. Gastroenterology 1972; 62:626–631.
21. Deveney CW, Deveney KS, Jaffe BM, et al. Use of calcium and secretin in the diagnosis of gastrinoma (Zollinger–Ellison syndrome). Ann Intern Med 1977; 87:680–686.
22. Ganguli PC, Polak JM, Pearse AGE, et al. Antral-gastrin cell hyperplasia in peptic ulcer disease. Lancet 1974; 1:583–586.
23. Bradley EL III, Isaacs J, Hersh T, et al. Nutritional consequences of total gastrectomy. Ann Surg 1975; 182:415–429.