Results of Surgical Management in 92 Consecutive Patients with Zollinger-Ellison Syndrome

SERGE BONFILS, M.D., JOHN H. LANDOR, M.D., MICHEL MIGNON, M.D., PHILIPPE HERVOIR, M.D.

From the Gastroenterological Research Unit, INSERM U. 10 Hopital Bichat Paris, France

Hosptial records and follow-up information on 92 patients with surgically proven Zollinger-Ellison syndrome have been reviewed, and data relating to symptomatology, age and sex incidence, pathologic findings, and early and late results of surgical procedures have been summarized. The postoperative mortality rate was 15%, and was adversely affected by previous peptic ulcer surgery, by the necessity of urgent operation for complications of peptic ulcer, and by employment of a procedure that failed to control acid secretion. Thirteen patients were found to have primary gastrinomas of the duodenum and an additional 13 patients had islet cell hyperplasia without evidence of frank neoplasm; prognosis in these two groups appears to be particularly favorable. Despite the current availability of effective nonoperative measures for control of gastric hypersecretion, surgical exploration is warranted in all patients to determine location and extent of tumor and to attempt to control the ulcer diathesis by resection of tumor. Long-term therapy with H_2 receptor antagonists is advised for patients whose hypersecretory state has not been alleviated by tumor resection or whose gastrinoma cannot be removed. Total gastrectomy is still indicated in patients whose tumors are not amenable to resection and who are resistant to, or cannot follow, a rigid medical regimen.

IT HAS NOW BEEN more than a quarter of a century since the description by Zollinger and Ellison[1] of the syndrome which bears their names. Early in that period, total gastrectomy became the procedure of choice in the treatment of nearly all patients, and the long-term results of total gastrectomy have become the standard by which other forms of therapy must be measured. The development of the H_2 receptor antagonists, however, and the recognition that these potent antisecretory drugs can effectively inhibit gastric secretion in patients with Zollinger-Ellison Syndrome (ZES)[2,3] have fostered new, promising approaches to the therapy of this complex and potentially lethal condition.[4]

In order to assess the effectiveness of new modes of therapy it is essential that an accurate appraisal of the natural history of the syndrome and the results of current therapy be made. Unfortunately, the study of ZES is made difficult by its relative rarity, a circumstance which has made it necessary to rely on data from relatively small series of patients, from individual case reports, and from collected groups of patients amassed from many different centers. Because we have been fortunate in being able to study a considerable number of patients in one institution it seemed desirable to review our experience with these patients in an attempt to characterize various aspects of the disease and to evaluate the results of surgical therapy.

Methods

From 1960 to 1976, the diagnosis of ZES was made in 92 patients who were evaluated at Hopital Bichat and were then treated surgically. The diagnosis was made by a combination of clinical and laboratory criteria and was confirmed at operation by the finding of islet cell tumors (79 patients) or islet cell hyperplasia (13 patients). The majority of patients in this series underwent surgical therapy at Hopital Bichat but approximately one-third were seen for diagnostic evaluation only, surgical therapy being undertaken at other hospitals. An attempt was made to follow all of the patients at least yearly, including those operated on at other hospitals; follow-up studies, when possible, were carried out in the Gastroenterology Department at Bichat and, in other instances, by correspondence with the patient or his physician. Initial assessment and routine follow-up consisted of clinical evaluation, serum gastrin, and one-hour basal gastric analysis in those patients in whom total gastrectomy had not been performed. Other studies, such as x-rays and secretin challenge were done when indicated. In the early years of the study, bioassay was used to document hypergastrinemia[5] but more recently (beginning in 1971) gastrin

Correspondence: John H. Landor, M.D., Department of Surgery, CMDNJ-Rutgers Medical School, Piscataway, New Jersey 08854.

Reprint requests: Professor Serge Bonfils, Unite de Recherches de Gastroenterologie (U.10), Hopital Bichat, 170, Boulevard Ney, 75877 Paris Cedex 18, France.

Submitted for publication: April 28, 1981.

0003-4932/81/1200/0692 $00.80

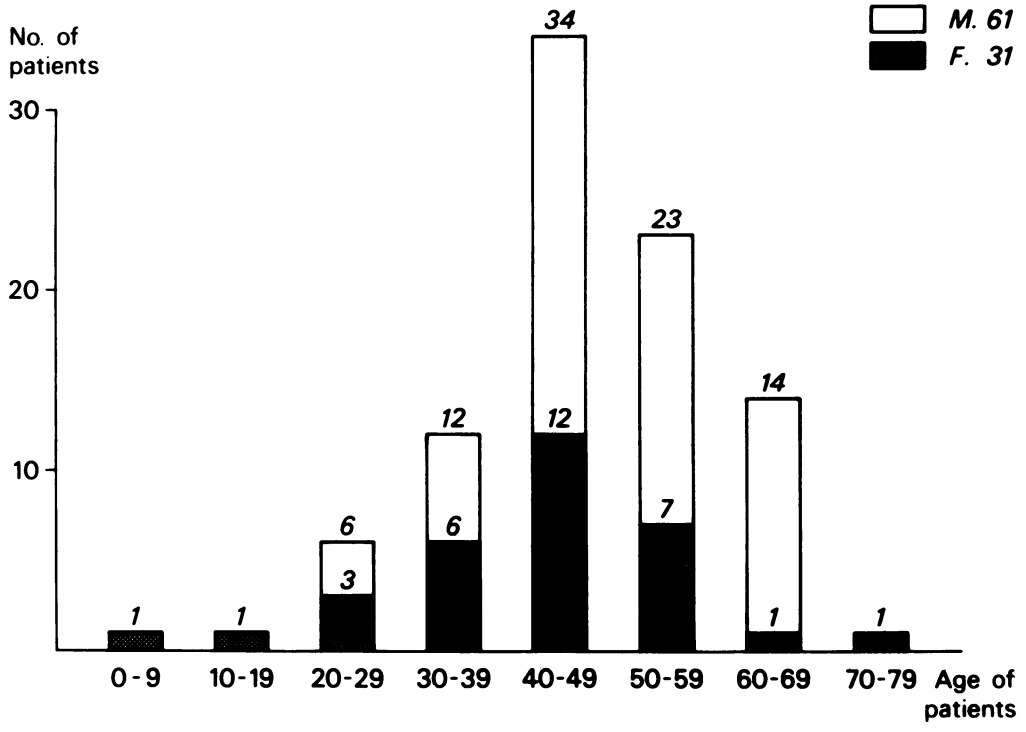

FIG. 1. Age and sex distribution of 92 patients with Zollinger - Ellison Syndrome.

levels have been determined by radioimmunoassay according to the method of Yalow and Berson.[6]

In 1979 the records of all patients were reviewed and pertinent data were tabulated. Information regarding initial assessment, operative findings, operation performed and the early results of surgery was available on all 92 patients. Eighty patients had been operated on five or more years previously and, of these, 14 were lost to follow-up. A five-or-more-year follow-up is thus available on 66 patients with ZES followed in a single institution.

Results

Initial Evaluation

The age and sex distribution are seen in Figure 1. The male:female ratio was 2:1 and the peak incidence was in the fifth decade; two patients were younger than twenty years and only one was older than 69 years. Principal modes of clinical presentation are listed in Table 1. It can be seen that the vast majority of patients presented with manifestations of peptic ulcer disease. In 26 of the 39 patients with primary peptic ulcer the ulcer was in an atypical location; seven patients were operated on emergently because of complications of primary ulcers and eight were operated on for complications of recurrent ulcer after previous peptic ulcer surgery. Seventeen patients had diarrhea as the principal manifestation (an additional 44 had diarrhea accompanying ulcer distress). In 11 patients the diagnosis was made on investigation of patients with MEA-1 syndrome whose predominant symptoms were related to endocrine disease other than gastrinoma, most often hyperparathyroidism. A total of 19 MEA-1 patients was found to have endocrine lesions including adrenocortical, thyroid, pituitary and β cell islet tumors. Basal secretion was measured in 43 patients who had not had previous ulcer surgery and in 22 patients who had had previous gastric operations; 81% of the former group secreted in excess of 15 mEq HCl per hour and 73% of the latter group secreted in excess of 5 mEq HCl per hour. Fasting serum gastrin determination was carried out in 34 patients and was found to be higher than normal (100 pg/ml) in all but six.

Operations, Findings and Early Results

Total gastrectomy was performed in virtually all of the patients operated on at Hopital Bichat, but a few

TABLE 1. *Predominant Clinical Manifestations at Time of Diagnosis in 92 Patients with Zollinger–Ellison Syndrome*

	Number of Patients
Primary peptic ulcer	39
Recurrent peptic ulcer after previous operation(s)	24
Diarrhea	17
Manifestations of MEA-1 other than ulcer of diarrhea	11
Abdominal mass and cachexia	1
TOTAL	92

TABLE 2. *Pathologic Findings at Operation in 92 Patients with Zollinger–Ellison Syndrome*

Primary Lesions	Without Metastases	With Metastases
Pancreatic tumor	31	23
Duodenal tumor	8	5
Gastric tumor		1
Islet cell hyperplasia	13	
Unknown		11
Total	52	40

patients underwent other procedures such as resection of tumor alone. When no tumor was found after careful exploration, a generous resection of the tail of the pancreas was carried out in addition to total gastrectomy so that histologic evaluation of the pancreas could be made. Operations performed at other hospitals were more varied. In all, total gastrectomy was carried out in 57 patients and other ulcer operations such as subtotal gastrectomy were done in 21; these resections were accompanied by biopsy or resection of tumor. A variety of nongastric procedures was utilized in varying circumstances in the remaining 14 patients.

The findings at operation are given in Table 2. Fifty-four patients had obvious pancreatic tumor, and metastases were present in 23 of these. Thirteen duodenal tumors were identified, five of which were associated with obvious metastases. Thirteen patients with no grossly visible tumor had histologic proof of islet cell hyperplasia. Eleven patients were found to have metastases without a discoverable primary neoplasm and one patient had a primary gastric tumor with metastases.

There were 14 postoperative deaths (15%). After elective total gastrectomy there were no deaths among patients who had not had previous ulcer operations, but four deaths among those who had; total gastrectomy undertaken urgently for complications of peptic ulcer was followed by death in four instances. Operations other than total gastrectomy were followed by death in three cases when the operation was elective and three cases when it was emergent; four of these deaths came as a direct result of poor choice of procedure, for they were caused by complications arising from persistent, severe ulcer diathesis in the immediate postoperative period.

Long-term Results

For the 66 patients followed for five years the absolute overall survival rate was 45.5%. When actuarial methods were used to project yearly survival the five-year survival for the entire group was 57% and at ten years the figure was 50% (Fig. 2). The absolute five-year survival rate among the patients treated by total gastrectomy was 47.6%, among those treated by other gastric operations it was 35.7%, and among those having

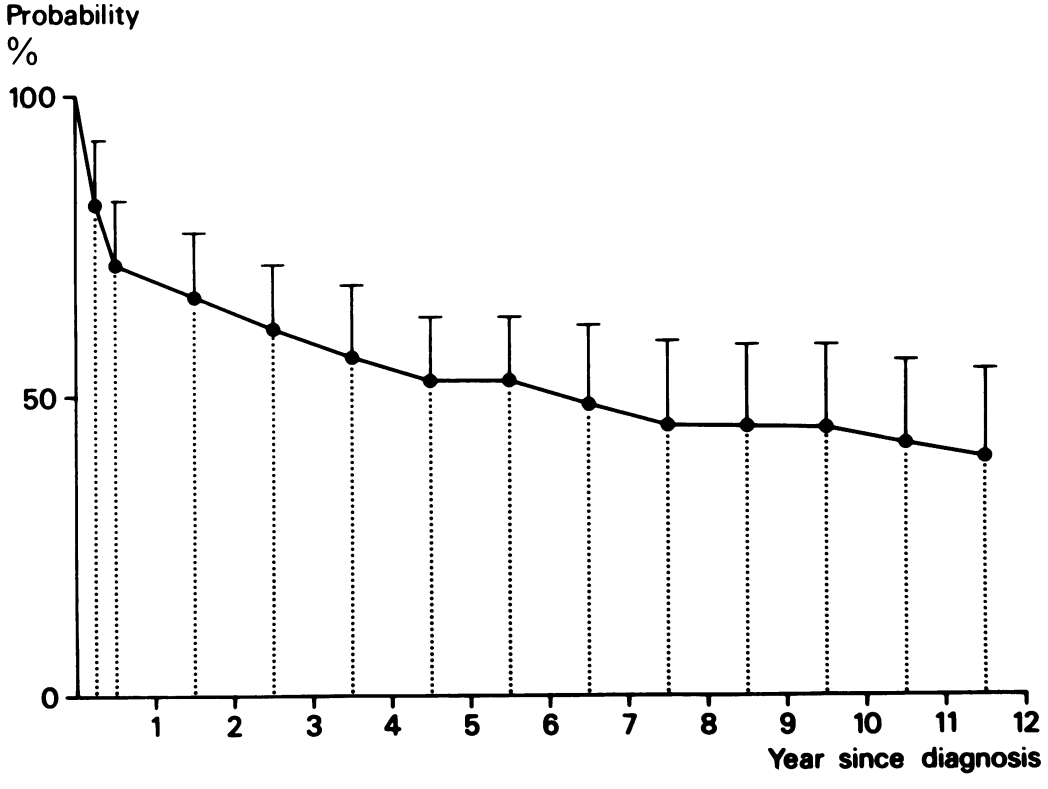

FIG. 2. Actuarial estimate of survival up to 11.5 years among 92 patients with Zollinger-Ellison Syndrome.

TABLE 3. *Preoperative Serum Gastrin Level (pg/ml), Latest Postoperative Gastrin Levels, Operative Procedures and Follow-up in 13 Patients with Primary Duodenal Gastrinoma*

	Gastrin Level				
	Preoperative	Postoperative	Operative Procedure	Alive	Dead
1			Excision, part. gast.*	14 yr (late total gastrectomy)	
2			Total gast.*	1 yr	
3			Excision, total gast.		4 yr (suicide)
4			Excision, part. gast.		7 yr (ulcer)
5			Excision, total gast.	11 yr	
6			Excision, total gast.	10 yr	
7	305	25 (1 yr)	Excision, total gast.	2 yr	
8		65 (½ yr)	Excision, part. gast.*	6 yr (late total gast.)	
9	595	2400 (4 yr)	Excision, total gast.*	4 yr	
10	345	42 (2 yr)	Excision, total gast.	2 yr	
11	400	80 (2 yr)	Excision	2 yr	
12	340	75 (3 yr)	Excision	3 yr	
13	260	82 (1 yr)	Excision	1 yr	

* Cases in which involved nodes were removed. Cases 1 and 8 had total gastrectomy 11 yrs, and ½ yr. after original operation.

nongastric procedures it was 50%. Of the 27 deaths known to have occurred after the immediate postoperative period, 19 were related to tumor extension by local or metastatic spread, three were due to the ravages of recurrent peptic ulcer in patients who had not had total gastrectomy, and one was caused by a hypercalcemic crisis (see below); the remainder were caused by conditions other than ZES (suicide in two and cirrhosis in two). Three categories of patients (those with duodenal tumor, those without demonstrable tumor but with islet cell hyperplasia, and those in whom a curative attempt at surgical extirpation of neoplasm had been made) have been analyzed separately to evaluate prognosis in these particular groups.

Thirteen patients had identifiable duodenal primary tumors and were treated by excision of all recognizable tumor (Table 3); in the earlier years, tumor excision was accompanied by gastrectomy but in the most recent three patients, whose secretion was controllable with cimetidine, gastrectomy was not performed. Excision of the primary tumor was accomplished in all but one patient and one or more lymph nodes were removed in four patients. Preoperative gastrin levels are available in six patients who have had postoperative gastrin determination done from one to four years after operation; the single patient with the four-year follow-up had neither an early nor a late fall in the serum gastrin level but the other five patients had early postoperative declines to normal levels which have been sustained from one to three years. All three patients treated in the early years with less than a total gastrectomy developed recurrent ulceration. One patient underwent a total gastrectomy 11 years after the initial procedure, at which time liver metastases were found and the serum gastrin level was 1000 pg/ml; three years later, the serum gastrin level was 100 pg/ml and the patient was well. The second patient died of a perforated ulcer seven years after operation. The third patient underwent a total gastrectomy for recurrence just six months after operation, was found to have liver metastases, and was known to be well five years later. There was one death from suicide. Thus, in the entire group of 13 patients, there was one death from ZES and 11 patients were found to be well from one to 14 years (mean: 5 years) after initial diagnosis and therapy.

In 13 patients treated by total gastrectomy no tumor was found and pathologic examination of the resected tail of the pancreas revealed islet cell hyperplasia. All of these patients had the classic stigmata of ZES including excessively high levels of secretion and elevated levels of gastrin determined either by bioassay or by radioimmunoassay. Four patients had had one previous operation for peptic ulcer and five patients had had two or more previous ulcer operations. All three patients in whom immunoassayable gastrin was determined four, seven and eight years after operation had elevated basal serum gastrin levels, and an additional patient (the only one to have had a postoperative secretin challenge) had a rise in the serum gastrin level in response to intravenous secretin. Among these 13 patients there was only one early postoperative death and one death from cirrhosis with bleeding esophageal varices two years after total gastrectomy. The mean follow-up period of the remaining 11 patients is close to seven years (1–15 years) and all were well at last follow-up examination.

Twenty patients with nonduodenal neoplasms had attempted complete removal of the primary tumor and any metastases that were present. These operations included pancreaticoduodenectomies and various lesser procedures ranging from excision of a small pancreatic

nodule to resection of the body and tail of the pancreas. Tumor resection alone was performed in seven patients and an accompanying gastrectomy was performed in 13 (total gastrectomy in ten). The two patients in the former group who died in the postoperative period had rapidly recurrent peptic ulcer disease. An additional two patients required total gastrectomy for recurrence and one of these died of complications after operation. Three patients were alive and well at four, four and 11 years after initial operation, respectively. Among the 13 patients subjected to gastrectomy as well as to tumor resection there were three postoperative deaths, two of which occurred in patients who had pancreaticoduodenectomy. Of the four late deaths, three were caused by tumor extension and one was caused by hypercalcemic crisis in a patient with MEA-1 syndrome. The latter patient had had unsuccessful neck exploration and was found at autopsy examination to have a mediastinal parathyroid adenoma but no residual pancreatic tumor. Six patients in this group are known to have survived from two to 12 years.

Discussion

The age and sex distribution, presenting symptoms, laboratory data and survival figures are not greatly different from those found in other large groups of patients with ZES.[7-9] As noticed by others, not all patients were found to have excessively high levels of serum gastrin and, indeed, in six of our patients the values were well within normal limits. In patients with normal basal gastrin the clinical characteristics of ZES as well as an excessively high rate of basal secretion (found in virtually all of our patients) should prompt the clinician to seek preoperative confirmation of the diagnosis of ZES through the use of provocative tests with secretin and/or calcium.[9,10]

Examination of the postoperative deaths in this series suggests that total gastrectomy is associated with a higher risk when undertaken in patients with previous gastric operations and in patients being operated on for acute hemorrhage or perforation. Four of the six deaths that occurred after lesser gastric procedures came as a direct result of the complications of rapidly recurrent peptic disease and these procedures were clearly ill-advised. Now that effective antisecretory agents such as the H_2 receptor antagonists are available, however, it is likely that such procedures can be undertaken in selected cases without incurring added risk, particularly if sensitivity to these agents has been determined preoperatively.

The relatively favorable prognosis of patients with gastrinomas of the duodenum has been noted by Oberhelman.[11] Though this was not found in the Zollinger-Ellison tumor registry series,[12] it is certainly confirmed in the present series. Of particular interest is the return to normal of the serum gastrin level after excision of tumor in five of the six patients in whom these measurements were done. These figures allow cautious optimism in regard to patients with primary lesions of the duodenum, and we feel that further trial of tumor resection without gastrectomy is warranted in patients who have been shown to respond favorably to therapy with H_2 receptor antagonists.[13] Because of the very slow rate of progression of many of these tumors, only a very long follow-up will provide unequivocal evidence of cure, but these relatively short-term results clearly suggest the desirability of continuing to attempt cure by excision. The patient in this group who was found to have liver metastases at the time of total gastrectomy and then had a decrease in serum gastrin level is of interest in light of Friesen's suggestion that gastrectomy may lead to regression of metastatic disease;[14,15] however, laparotomy would be needed to verify tumor regression and, in any case, spontaneous regression cannot be ruled-out.

Another group with favorable prognosis appears to be those patients in whom only islet cell hyperplasia was found without gross evidence of neoplasm. Among these 13 patients, there have been only two deaths, and 11 patients were alive from one to 15 years after operation. Whether the cause of ZES can be attributed to islet cell hyperplasia alone[16] or whether such hyperplasia is simply another manifestation of the syndrome in patients with a hidden islet cell tumor[17] is not certain and cannot be settled by the data herein reported. It is possible that these patients had one or more small islet cell tumors not discovered at operation and only a thorough autopsy examination of such patients after years of follow-up could settle this question. Nevertheless, it is clear that patients who have no discoverable neoplasm have a strong likelihood of surviving for long periods of time.

The group of 20 patients in whom an attempt was made to resect pancreatic tumors with or without lymph node metastases is too small and disparate to allow any definite conclusion as to the efficacy of attempted curative resection of nonduodenal primary tumors. Long-term survival was not better (in fact was worse) than for the entire group of 92 patients. However, the fact that nine patients were alive at last follow-up and that six of these had survived for six, ten, ten, 11, 12 and 12 years, respectivley, suggests that curative resection may be of benefit when it can be done without adding appreciably to the operative risk. Four patients in this group had pancreaticoduodenectomy, two of whom died of postoperative complications, and we would not recommend such radical procedures in attempting to cure a neoplasm which often pursues an indolent course.

Almost all of the patients in our series were operated on before the advent of successful medical therapy for

ZES. It is clear from our results and those of others that total gastrectomy, particularly in the elective situation, can be performed with a low operative mortality rate and that it provides the permanent and certain protection against peptic ulceration that no other procedure can match. The introduction of H_2 receptor blocking agents, and the continuing development of more effective ones, has opened a new era in the therapeutic approach to ZES, however, and it seems likely that total gastrectomy will not be necessary in all cases. Richardson et al.[18] have even proposed, on the basis of experience with three patients, that vagotomy may facilitate the efficacy of these antisecretory agents. New approaches such as this must be considered experimental, however, until long-term follow-up in a large number of patients provides proof that they are at least as safe and effective as is total gastrectomy. This is particularly true in view of the fact that the H_2 receptor blocking agents are not effective in every patient, that some patients who respond favorably will later develop resistance to the agent,[19] and that unpleasant side effects are not infrequently encountered.

The proven effectiveness of antisecretory agents in the majority of patients with ZES cannot be denied, however, and this makes their use an attractive supplement to surgical therapy in selected cases. We believe that drug efficacy should be assessed in all patients with ZES and we currently prefer continuous 24-hour monitoring of intragastric acidity as the most reliable method to achieve this[20]; a satisfactory response is considered to be an intragastric pH above 1.5 maintained throughout 50% or more of the 24-hour period. We advise that all patients, both responders and nonresponders, be subjected to exploratory laparotomy to determine the location and extent of the gastrin-secreting neoplasm. Both primary tumor and identifiable lymph node metastases are excised when this can be accomplished without a radical procedure. In patients who have responded satisfactorily to H_2 receptor antagonists, total gastrectomy is not done; drug therapy is continued if the tumor has not been extirpated but, if the tumor has been removed and the serum gastrin level has returned to normal, antisecretory therapy is stopped and gastric secretion as well as serum gastrin are monitored at regular intervals. Patients who do not have an adequate response to H_2 receptor blocking agents are subjected to total gastrectomy at the initial operation whether or not tumor resection has been performed. All patients who have not had total gastrectomy must be followed carefully forever so that adequacy of control of gastric secretion can be assured and so that those who develop resistance to H_2 receptor antagonists can have total gastrectomy before peptic ulcer complications occur.

In patients who are considered possible candidates for drug therapy as a substitute for total gastrectomy a frank and open discussion of both alternatives and their implications is of vital importance. It should be clear to the patient that medical management requires a lifetime commitment to a strict regime that includes frequent monitoring of his gastric secretion as well as adherence to a rigid schedule of medication. There are patients who, for a variety of reasons, either cannot, or do not wish to, undertake this sort of permanent regimen. These patients must be offered permanent and reliable protection against the peptic ulcer diathesis of ZES by means of total gastrectomy.

References

1. Zollinger RM, Ellison EH. Primary peptic ulceration of the jejunum associated with islet cell tumors of the pancreas. Ann Surg 1955; 142:709-728.
2. Mainardi M, Maxwell V, Sturdevant RAL, Isenberg JI. Inhibition of gastric acid secretion by Metiamide in Zollinger-Ellison syndrome. Am J Dig Dis 1975; 20:280-281.
3. Blair EL, Grund ER, Miller IT, et al. Metiamide in the Zollinger-Ellison syndrome. Am J Dig Dis 1975; 20:1123-1130.
4. McCarthy DM. The place of surgery in the Zollinger-Ellison syndrome. N Engl J Med 1980; 302:1344-1347.
5. Dubrasquet M, Bonfils S, Bader JP, et al. Essai biologique des urines (test PSU) pour le diagnostic et la surveillance postopératoire du syndrome de Zollinger-Ellison. Acta Gastroenterol Belg 1973; 36:438-448.
6. Yalow RS, Berson SA. Radioimmunoassay of gastrin. Gastroenterology 1970; 58:1-14.
7. Ellison EH, Wilson SD. The Zollinger-Ellison syndrome: reappraisal and evaluation of 260 registered cases. Ann Surg 1964; 160:512-530.
8. Fox PS, Hofmann JW, Wilson SD, DeCosse JJ. Surgical management of the Zollinger-Ellison syndrome. Surg Clin North Am 1974; 54:395-407.
9. Deveney CW, Deveney KS, Way LW. The Zollinger-Ellison syndrome—23 years later. Ann Surg 1978; 188:384-393.
10. Mignon M, Accary JP, Bonfils S. Signification diagnostique du test à la sécrétine dans le syndrome de Zollinger-Ellison. Analyse de la réponse gastrinique et acide dans une série de 21 tests positifs. Gastroenterol Clin Biol 1977; 1:425-434.
11. Oberhelman HA, Jr. Excisional therapy for ulcerogenic tumors of the duodenum. Long-term results. Arch Surg 1972; 104:447-453.
12. Hofman JW, Fox PS, Wilson SD. Duodenal wall tumors and the Zollinger-Ellison syndrome. Arch Surg 1973; 107:334-339.
13. Bonfils S, Mignon M, Landor JH. Management of Zollinger-Ellison syndrome. N Engl J Med 1980; 303:942.
14. Friesen SR. Effect of total gastrectomy on the Zollinger-Ellison tumor: Observations by second-look procedures. Surgery 1967; 62:609-613.
15. Friesen SR. A gastric factor in the pathogenesis of the Zollinger-Ellison syndrome. Ann Surg 1968; 168:483-501.
16. Martin ED, Potet F. Pathology of tumours of the GI tract. Clin Gastroenterol 1974; 3:511-532.
17. Creutzfeldt W, Arnold R, Creutzfeldt C, Track NS. Pathomorphologic, biochemical, and diagnostic aspects of gastrinomas (Zollinger-Ellison syndrome). Hum Pathol 1975; 6:47-76.
18. Richardson CT, Feldman M, McClelland RN, et al. Effect of vagotomy in Zollinger-Ellison syndrome. Gastroenterology 1979; 77:682-686.
19. Bonfils S, Mignon M, Gratton J. Cimetidine treatment of acute and chronic Zollinger-Ellison syndrome. World J Surg 1979; 3:597-604.
20. Mignon M, Vallot T, Mayeur S, et al. Ranitidine and Cimetidine in Zollinger-Ellison syndrome. Br J Clin Pharmacol 1980; 10:173-174.