Zollinger-Ellison Syndrome

Spontaneous Regression of Advanced Intra-abdominal Metastases With 20 Year Survival

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A 35-year-old man with the Zollinger-Ellison syndrome who is alive and well 20 years following diagnosis at age 15, is represented. At the initial operation for a bleeding duodenal ulcer a ZE tumor of the pancreas also was excised. After two additional ineffective ulcer operations, total gastrectomy was performed. At that time, retroperitoneal and peripancreatic metastases were noted, and several were removed. Three years later at laparotomy, extensive hepatic metastases were biopsied as well. Spontaneous remission occurred and when re-explored at age 34, after 14 years, *no* metastases were identifiable in any area. The serum gastrin level has remained elevated, casting doubt upon its value as a criterion for evaluation of tumor recurrence or activity. Other additional interesting aspects are discussed. The importance of elimination of the acid-secreting cells by *total* gastrectomy is emphasized. The patient remains well.

IT HAS NOW BEEN 23 YEARS since Zollinger and Ellison[24] presented two cases of a new and interesting syndrome characterized by a nonbeta cell islet pancreatic tumor, marked by hypersecretion of gastric acid and an unrelenting ulcer diathesis. This intractable ulcer development was stubbornly resistant to conventional medical and surgical therapy. Additional cases were rapidly reported. As pertinent information accumulated, it became apparent that although these islet tumors were histologically benign, many behaved as malignant neoplasms, frequently metastasizing. Further, within several years it became apparent that the expedient of total gastrectomy was the preferred treatment if fatalities from ulcer complications were to be avoided.

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The causative agent was obviously elaborated by the pancreatic tumor. It's identity long remained obscure but was postulated as being a "gastrin-like substance."[10] Until the isolation of gastrin, this remained unproven.[14]

Additional investigators reported further ramifications. Wermer[18] and others early suspected involvement of multiple endocrine glands. This concept (MEA) has continued to be of great interest. In some patients other symptoms, notably watery diarrhea, were noted and thought to be the result of hyperacidity.[12]

In 1961 Davis and his associates[3] reported a classical case occurring in a 15-year-old boy. The diagnosis was proven at the initial operation in 1958. Over the next 20 years this patient demonstrated many of the incredible features of this tumor. This unusual neoplasm continues to elicit frequent discussion and ever-increasing interest, as well as some controversy. Our patient's 20-year survival reintroduces this fantastic subject.

Synopsis of Original Report[3]

On April 14, 1958 a 15-year-old, white boy was admitted for the first time to Norfolk General Hospital with the complaints of epigastric distress, occasional vomiting and intermittent diarrhea of five months' duration. A large duodenal ulcer was found, and medical management was begun. Two weeks later, a severe gastric hemorrhage occurred. Operation revealed a large, actively bleeding posterior duodenal ulcer just distal to the pylorus. An additional finding was a 5 cm ZE tumor in the pancreas, this was excised, and subtotal gastric resection with a Billroth II reconstruction was done.

Sixteen months later, massive gastric hemorrhage

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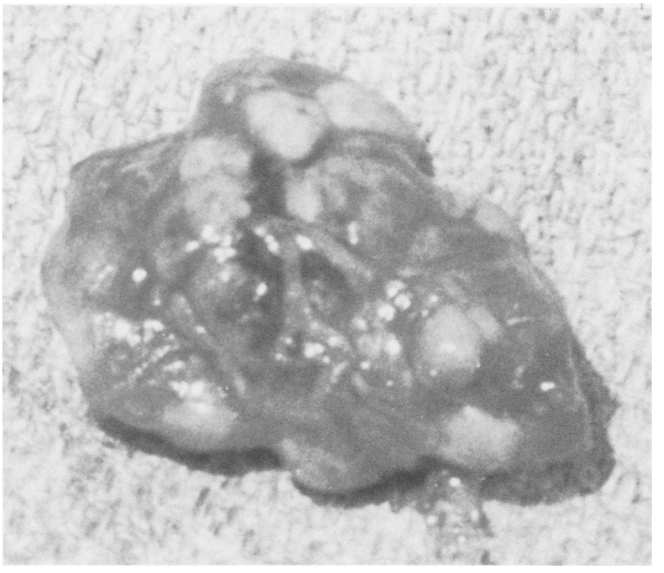

FIG. 1. Photograph of peripancreatic metastases removed in 1960. (Courtesy of Publisher)

again occurred. A large stomal ulcer was found at operation. It was resected, additional stomach was removed and truncal vagotomy was done. He recovered uneventfully.

Gastric hemorrhage developed again 10 months later. X-rays demonstrated a *new* jejunal ulcer on the proximal side of the most recent anastomosis. A Hollander insulin test was positive, and therefore a transthoracic vagotomy was performed. Recovery was unremarkable. The patient thrived, gaining 15 lbs. within 60 days, and radiologically the marginal ulcer healed.

After the original operation in 1958, Dr. Zollinger had been consulted and gave continued, enthusiastic and helpful advice. Accumulated experience by 1960 clearly indicated the treatment of choice to be complete gastric resection.

In September 1960, three months after transthoracic vagotomy, gastric hemorrhage again required admission to the hospital. When operated upon he was found to have a third stomal ulcer, as well as numerous retroperitoneal and peripancreatic masses ranging up to 5 cm in diameter. The liver was normal. The ulcer was resected, and a *total* gastrectomy was done employing a Roux-en-Y technique with an end-to-side esophagojejunostomy. Several large peripancreatic tumors were removed. Pathological examination confirmed them to be identical with the primary neoplasm removed two years previously (Fig. 1). Extracts from one of the tumors were found, in Zollinger's laboratory, to incite a vigorous acid response in Pavlov's pouch (Fig. 2); this was greater and longer sustained than with pure histamine.

The patient recovered uneventfully. There were no dietary problems, and growth and development were uninhibited. He served an apprenticeship as a butcher and then found employment.

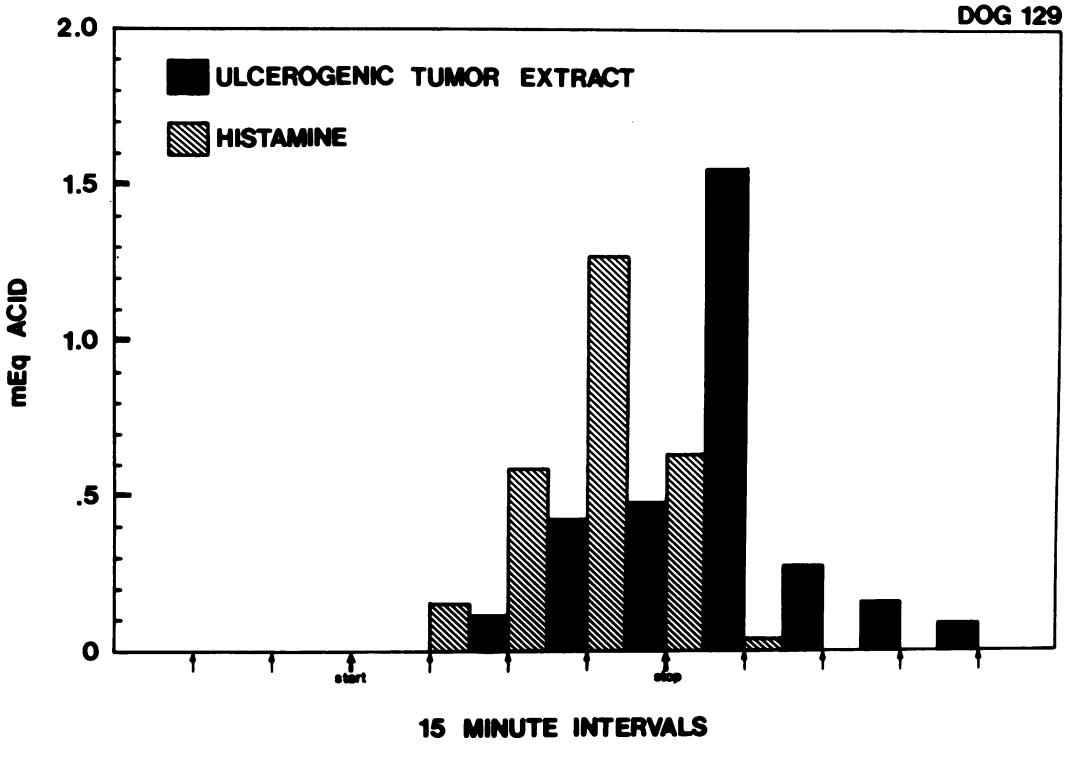

FIG. 2. Graph showing acid response to tumor extract injection in Pavlov's pouch (Zollinger's laboratory). (Courtesy of Publisher)

Review of Subsequent Course

Following total gastrectomy, the patient did well. At the time of the initial report[3] on December 5, 1961, 14 months postoperatively, there were no digestive symptoms and weight gain of approximately 20 lbs. had occurred. This trend continued until 2½ years after operation, when progressive upper abdominal pain developed and weight declined. Increasing hepatomegaly was noted. Large amounts of narcotic for pain relief were required. This general decline accelerated, and in May 1963 he developed fever, an expanding right upper quadrant mass and slight jaundice. Cachexia was evident. Laparotomy was necessary, and the large abdominal mass was found to consist of severe inflammation surrounding an empyema of the gallbladder. Additionally, a tremendously enlarged liver *filled* with innumerable small metastases was noted. In addition, the peripancreatic and retroperitoneal masses noted at his last operation in 1960 had greatly increased. The gallbladder contained purulent material, but no calculi were present. An hepatic biopsy confirmed metastases histologically similar to the previous islet tumor. A palliative cholecystostomy was done.

Postoperative recovery was prompt, but increasing pain required ever larger amounts of narcotics. After about eight months, however, this downward trend appeared to reverse, and a rather dramatic improvement began. There was rapid, steady weight gain, and the previously severe upper abdominal pain lessened. There was a sharp reduction in narcotic requirements coincidental with his improvement in health. Blood chemistry and chest x-rays were normal. Spontaneous remission was considered. Despite these encouraging notes, a liver scan done February 14, 1965 showed multiple small defects consistent with metastases. Twenty months following liver biopsy and palliative cholecystostomy, there had been a weight gain of 20 lbs., his digestion was normal and there was no evidence of hepatomegaly.

In March 1965 he was one of eight individuals to be presented by Wilson and Ellison[20] before the Central Surgical Association, all of whom had undergone total gastrectomy at 15 years of age or under for treatment of the ZES. The purpose of their review was to evaluate possible adverse effects on growth and development resulting from complete stomach removal in children. This study demonstrated no such harmful consequences.

After several years of improvement, our patient's personal problems magnified, and drug dependency again developed. He subsequently struggled to reduce his narcotic demands, and during this period his weight declined to as low as 110 lbs. Gradually, primarily by his own effort, he eliminated the drug habit. In May 1967 he weighed 158 lbs., and his health was excellent. A liver scan was negative.

Bioassay of his blood in Ellison's laboratory at Marquette University in 1968 was positive for a "gastric secretagogue." Two years later, a serum gastrin level in Wilson's laboratory at the University of Wisconsin revealed a level of 8200 pg/ml (normal less than 500). Six months later a new assay on the same specimen showed 15,000 pg/ml. In 1974, blood sent to the Mayo Clinic revealed a gastrin level of 471 pg/ml (normal less than 150). Despite the hypergastrinemia, he remained healthy.

In July 1977 recurrent episodes of right upper quadrant pain suggested biliary colic. These increased in frequency and severity. The gallbladder failed to opacify on sustained dosage. Chest x-rays and liver scan were negative. The blood gastrin level remained elevated; several values in excess of 2000 pg/ml (normal less than 300) were obtained.

Persistent abdominal pain necessitated readmission to the Medical Centers Hospital in September 1977. At that time, abdominal examination was negative. Extensive laboratory data, including alkaline phosphatase, were negative except for a slightly elevated bilirubin. A chest x-ray showed no metastases, and a liver scan was normal.

Abdominal exploration revealed multiple calculi within both a severely scarred gallbladder and a markedly dilated common bile duct. The liver showed *no evidence* of metastatic disease (Fig. 3). *No* masses were detected within the pancreas, the peripancreatic or retroperitoneal regions (Fig. 4). In the suprarenal regions bilaterally, soft, rounded, thickened areas were palpated. Cholecystectomy and choledocholithotomy were performed. An operating room cholangiogram was normal. Pathological examination showed chronic cholecystitis and cholelithiasis. The cystic duct lymph node removed with the gallbladder was hyperplastic.

The patient's postoperative course was uneventful. A postoperative blood gastrin level of 3453 pg/ml (normal less than 300) was disturbing. He has, however, remained totally asymptomatic for over one year. His most recent blood gastrin level, obtained in November 1978, was 1390 pg/ml.

Discussion

Since the original report,[24] inconsistencies and some confusion have shrouded the picture. Many unusual and complex characteristics have been reported. Twenty year survival with documented regression of metastases proven at laparotomy 17 years earlier is most unusual. Although the incidence of multiple endocrine neoplasms, type I (MEA I), associated with the

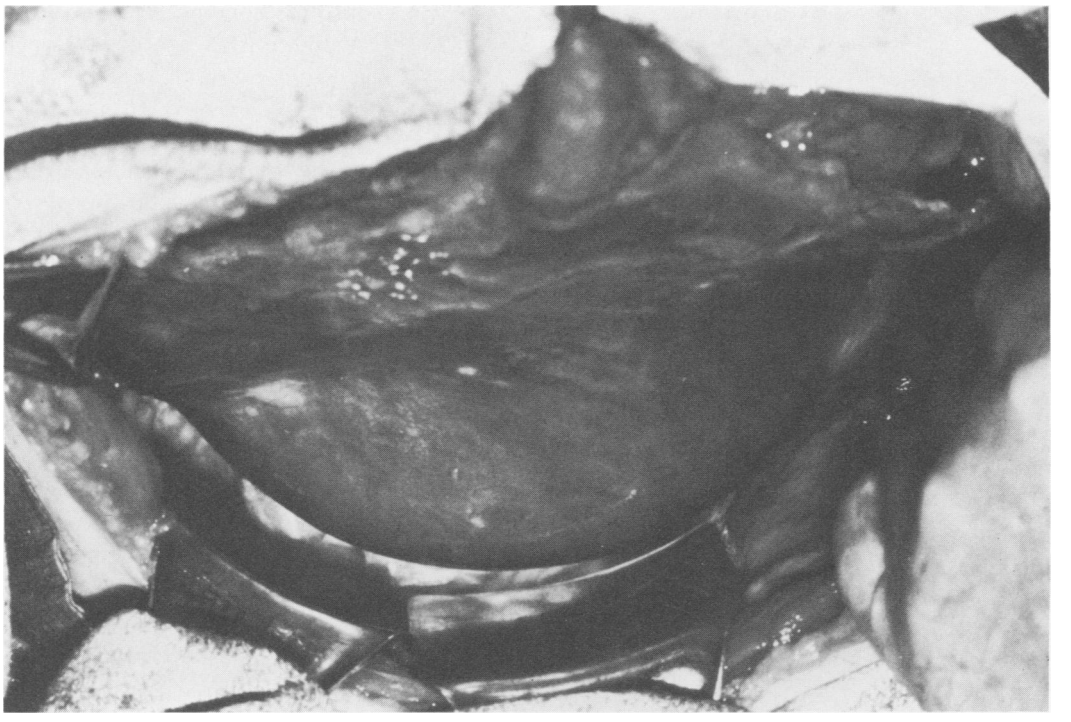

FIG. 3. Photograph of liver at last operation, free of metastases (1977).

ZES may be as high as 48%,[5] this patient has shown no clinical evidence of hyperparathyroidism or problems involving the pituitary, adrenal or thyroid glands. The persistence of high serum levels of gastrin, felt by many[1,9,23] to be of prognostic significance, contributes to the confusion.

The purpose of this updated report is to again direct attention to certain interesting facets of this disease which this patient demonstrates, including long-term survival and proven spontaneous tumor regression. The importance of *total gastrectomy* in treatment is emphasized.

Long-term Survival

The first patient operated upon by Zollinger in 1954 had lymph node metastases. She remains alive and well, 24 years after *total* gastrectomy.[23,24] Many[9,23] have commented on the classically slow growth of the tumor. Jordan,[13] the Deveneys and Way[5] and Thompson et al.[17] have reported long-term survival in patients with extensive metastases. Seven children with metastatic disease recorded by Wilson et al.[22] were living 2–13 years after total gastrectomy. Our patient was included in this series.

Tumor Regression

Although spontaneous tumor regression has been noted by many, its possible relationship to total gastrectomy is controversial. Melnyk, Dunphy and associates[15] reported the first case of spontaneous remission, which had continued for 20 months following laparotomy and single lymph node biopsy. An invasive islet cell carcinoma of the head of the pancreas with gastric extension prevented inclusion of total gastrectomy at the time of operation.

Friesen[7,8,9] believes that tumor regression is the result of total gastrectomy. Four such patients who subsequently underwent "second look" laparotomies revealed absence of previously documented tumor. Wilson and associates noted that "lack of progression" is easier to determine objectively than "evidence of regression." In a review of the Zollinger-Ellison Tumor Registry, Fox et al.[6] were able to find only four cases of documented regression out of 137 patients treated by total gastrectomy. Thompson et al.[16] and Hardy and Doolittle,[11] as well as the Deveneys and Way,[5] have not observed tumor regression following total gastrectomy. Our case adds further confusion.[3] At the time of total gastric resection no hepatic metastases could be found, although there was proven spread to other areas. Three years later, there was extensive *hepatic* involvement documented by biopsy. Laparotomy performed 14 years later demonstrated *no* tumor at any level.

Postgastrectomy Serum Gastrin Level

The significance of an elevated serum gastrin level following total gastrectomy remains unclear. Isenberg

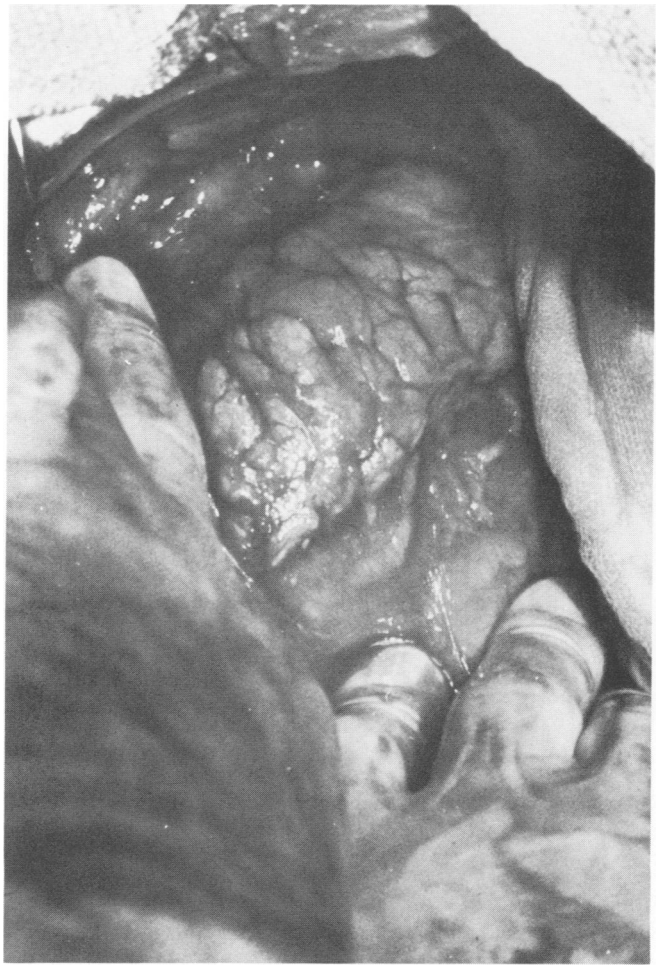

FIG. 4. Photograph of pancreatic and peripancreatic region, free of metastases (1977).

et al.[12] believe that total gastrectomy does not usually produce diminution of the serum gastrin level. In addition others[5] have found postoperative gastrin levels to be of no prognostic value. Furthermore, Thompson and his colleagues observed that hypergastrinemia *per se* produced no symptoms after total gastrectomy in patients with metastases.[16] Some have expressed a different opinion and believe that serum gastrin determinations following total gastrectomy are valuable in recognizing residual tumor and in providing a basis for judging prognosis.[6,9,23]

In our case, the serum gastrin level has remained significantly elevated despite *total* gastric resection 17 years previously. Even more interesting are the high gastrin levels in the absence of demonstrable tumor after proven extensive metastases.

Treatment

Total gastrectomy is the treatment of choice whether or not there are metastases, regardless of any other considerations.[3,5,6,7,11,12,17,21] Some have excepted the rare instance when a *solitary*, *resectable* tumor of the duodenum or pancreas is discovered and decrease in acid output is documented during the operation.[5,12,17] In our case, at the initial operation a single ZE tumor was found in the pancreas and removed. Two years later when total gastric resection was done, metastatic disease was proven to have developed, casting some doubt on the efficacy of *local* removal only.[3] In patients with more advanced disease, the elimination of as much neoplastic tissue as feasible in addition to total gastrectomy seems logical.[7,11,17] Some are now performing total gastrectomy without positive tissue diagnosis or even demonstrable tumor provided specific laboratory data[2] are positive.[5,12]

Data collected by the ZE Tumor Registry strikingly reveals that any gastric operation less than total gastrectomy results in significantly reduced immediate and long-term success.[6] The survival following total gastrectomy in 137 patients was 75% after one year and 42% after ten years. In contrast, survival following lesser gastric operations in 130 patients was 51% after one year and 18% after ten years. In 127 patients with proven liver metastases the ten year survival rate was 30% following total gastrectomy and no survivors following lesser gastric procedures. Documented evidence of regression has occurred *only* in patients upon whom a total gastrectomy has been performed.[8]

Control of the ulcer diathesis by total gastrectomy is obviously accomplished by elimination of the acid-secreting cells. Recently the stomach's role as the "end-target" has been amplified by the interesting cases of Wiersinga and Tytgat[19] and of Desai and Antia.[4] The former reported spontaneous elimination of acid hypersecretion and peptic ulcer disease in a ZE patient whose gastric mucosal lining was destroyed by intercurrent disease. The high gastrin levels were unchanged by this event. Desai's patient developed spontaneous persistent achlorhydria when severe atrophic gastritis developed. Further, the current use of the histamine H-2 receptor antagonist agent, cimetidine, to control the symptoms of the ZES adds another dimension substantiating the importance of parietal cell elimination or blockage in treatment.[5,8] Friesen[8] noted that cimetidine apparently has no effect on the serum gastrin level.

The mechanism whereby *total* gastrectomy possibly influences tumor growth is more controversial. Friesen[7] and Fox et al.[6] suggest a "gastric feedback" effect and cite comparative results favoring total gastrectomy over lesser procedures in support of this theory. On the other hand, Bradley and Galambos[2] explain the possible beneficial effect of tumor regression following total gastrectomy on the basis of suppression of endogenous secretin release due to absence of acid in the small intestine.

Conclusion

This second report updating this case provides further evidence of the vagaries of this fascinating tumor. The importance of total gastrectomy in its treatment at all levels is emphasized.

References

1. Bradley, E. L., III and Galambos, J. T.: Failure of Secretin Feedback Loop in the Zollinger-Ellison Syndrome? The "Gastric Factor" Revisited. Am. J. Dig. Dis. 17:939, 1972.
2. Bradley, E. L., III and Galambos, J. T.: Diagnosis of Gastrinoma by the Secretin Suppression Test. Surg. Gynecol. Obstet. 143:784, 1976.
3. Davis, C. E., Jr., Smith, P. Jr. and Davalos, X. S.: Ulcerogenic Tumor of the Pancreas. Ann. Surg. 155:669, 1962.
4. Desai, H. G. and Antia, F. P.: Spontaneous Achlorhydria with Atrophic Gastritis in the Zollinger-Ellison Syndrome. Gut, 10:935, 1969.
5. Deveney, C. W., Deveney, K. S. and Way, L. W.: The Zollinger-Ellison Syndrome—23 Years Later. Ann. Surg. 188: 384, 1978.
6. Fox, P. S., Hofmann, J. W., Decosse, J. J. and Wilson, S. D.: The Influence of Total Gastrectomy on Survival in Malignant Zollinger-Ellison Tumors. Ann. Surg., 180:558, 1974.
7. Friesen, S. R.: Zollinger-Ellison Syndrome. Curr. Probl. Surg. April 1972.
8. Friesen, S. R.: Discussion of reference 5.
9. Friesen, S. R., Bolinger, R. E., Pearse, A. G. E. and McGuigan, J. E.: Serum Gastrin Levels in Malignant Zollinger-Ellison Syndrome after Total Gastrectomy and Hypophysectomy. Ann. Surg., 172:504, 1972.
10. Gregory, R. A., Tracy, H. J., French, J. M. and Sircus, W.: Extraction of a Gastrin-Like Substance From a Pancreatic Tumor in a Case of Zollinger-Ellison Syndrome. Lancet, 1: 1045, 1960.
11. Hardy, J. D. and Doolittle, P. D.: Zollinger-Ellison Syndrome: Special Consideration. Ann. Surg., 185:661, 1977.
12. Isenberg, J. E., Walsh, J. H. and Grossman, M. I.: Zollinger-Ellison Syndrome. Gastroenterology, 65:140, 1973.
13. Jordan, G. L., Jr.: Discussion of reference 11.
14. McGuigan, J. E. and Trudeau, W. L.: Immunochemical Measurement of Elevated Levels of Gastrin in the Serum of Patients with Pancreatic Tumors of the Zollinger-Ellison Variety. N. Engl. J. Med., 278:1308, 1968.
15. Melnyk, C. S., Krippaehne, W. W., Benson, J. A., Jr. and Dunphy, J. E.: Spontaneous Remission of Zollinger-Ellison Syndrome. Arch. Intern. Med., 115:42, 1965.
16. Thompson, J. C., Reeder, D. D. and Bunchman, H. H.: Clinical Role of Serum Gastrin Measurements in the Zollinger-Ellison Synrome. Am. J. Surg., 124:250, 1972.
17. Thompson, J. C., Reeder, D. D., Villar, H. V. and Fender, H. R.: Natural History and Experience with Diagnosis and Treatment of the Zollinger-Ellison Syndrome. Surg. Gynecol. Obstet., 140:721, 1975.
18. Wermer, P.: Genetic Aspects of Adenomatoses of Endocrine Glands. Am. J. Med., 16:363, 1954.
19. Wiersinga, W. M. and Tytgat, G. N.: Clinical Recovery Owing to Target Parietal Cell Failure in a Patient with Zollinger-Ellison Syndrome. Gastroenterology, 73:1413, 1977.
20. Wilson, S. D. and Ellison, E. H.: Total Gastric Resection in Children with the Zollinger-Ellison Syndrome. Arch. Surg., 91:165, 1965.
21. Wilson, S. D. and Ellison, E. H.: Survival in Patients with the Zollinger-Ellison Syndrome Treated by Total Gastrectomy. Am. J. Surg., 111:787, 1966.
22. Wilson, S. D., Schulte, W. J. and Meade, R. C.: Longevity Studies Following Total Gastrectomy, in Children with the Zollinger-Ellison Syndrome. Arch. Surg., 103:108, 1971.
23. Zollinger, R. M.: The ulcerogenic (Zollinger-Ellison) syndrome. *In* Friesen, S. R. (ed.): Surgical Endocrinology, Clinical Syndromes. Philadelphia, J. B. Lippincott Co., pp. 203–214, 1978.
24. Zollinger, R. M. and Ellison, E. H.: Primary Peptic Ulcerations of the Jejunum Associated with Islet Cell Tumors of the Pancreas. Ann. Surg., 142:709, 1955.

Note to the reader: Please report all documented cases to Stuart D. Wilson, M.D., Zollinger-Ellison Tumor Registry, Division of Surgery, The Medical College of Wisconsin, Milwaukee, Wisconsin 53226.

Discussion

DR. JOHN L. SAWYERS (Nashville, Tennessee): This report provides us with a 20 year follow-up of one of the first patients recognized to have the Zollinger-Ellison syndrome. Many interesting questions have been raised by this report.

Dr. Warren Cole, who is attending this meeting, was the first prominent surgeon to document spontaneous regression of malignant tumors. There appears to be no question that spontaneous regression occurred in this patient. Was regression influenced by total gastrectomy? Dr. Stan Friesen has been trying to tell us for several years that total gastrectomy may result in regression of metastasis from a Z-E tumor, and has at least four such patients.

Most surgeons would agree that total gastrectomy will at least slow down the growth of metastasis from Z-E tumors.

Another interesting question is the significance of persistently elevated serum gastrin levels. Some surgeons think serum gastrin levels are prognostic regarding tumor metastasis, but others have found postoperative gastrin levels to have no prognostic value. Certainly, this patient, with continued elevation of serum gastrin levels, falls in the latter category.

This patient does point out clearly the value of total gastrectomy for patients with Zollinger-Ellison tumors, regardless of the presence or absence of metastasis. Many gastroenterologists are using cimetidine to treat patients with Zollinger-Ellison tumors. This trend should be discouraged. Cimetidine may be of value in preparing the Z-E patient for total gastrectomy, but nothing is known regarding the effect of cimetidine on tumor regression.

I hope that Drs. Davis and Vansant will continue to bring us periodic reports regarding this patient.

DR. JONATHAN A. VAN HEERDEN (Rochester, Minnesota): This presentation vividly outlines the vagaries of endocrine tumors in general, for they are indeed different to the nonendocrine malignancies in behavior. There is little doubt that a fair percentage of malignant endocrine tumors are fairly well tolerated by their hosts, in a state of virtual symbiosis. I'm sure we have all had the experience of following for long periods, up to years, those patients who are totally well with diffuse hepatic metastases secondary to, for example, carcinoid tumor, medullary carcinoma of the thyroid, and the Zollinger-Ellison syndrome. One must, therefore, wonder about the role of immunological tolerance in these patients, and whether this is a contributing factor to the documented cases of spontaneous regression of tumor, as here described.

The theory that removal of the stomach aids tumor regression is certainly suggested statistically, as so well outlined by Dr. Davis, but is suppositional at best.