Refer to: Sanchez RE, Longmire WP Jr, Passaro E Jr: Acid secretion and serum gastrin levels in the Zollinger-Ellison syndrome. Calif Med 116:1-7, Jun 1972

California Medicine
THE WESTERN JOURNAL OF MEDICINE

Acid Secretion and Serum Gastrin Levels In the Zollinger-Ellison Syndrome

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■ *Thirteen cases of patients with the Zollinger-Ellison syndrome were reviewed. In two cases the diagnosis was made by incidental biopsy of small liver nodules at operation for peptic ulcer disease.*

Seven patients had gastric secretory tests which showed a basal acid output to maximum acid output ratio of more than 65 percent. Five patients had BAO:MAO *ratios less than 50 percent.*

A 30-month interval between incidental discovery of tumor and clinically evident disease was observed in two patients. Recurrence of symptoms after excision of tumor was noted after a similar interval in another case.

Serum gastrin levels, before total gastrectomy, were elevated in all cases. The lowest preoperative level in this series of patients was 550 picograms per ml (normal 100 to 150 picograms). They were diagnostic in two patients with normal gastric secretory studies. The levels fell to normal following total gastrectomy in six patients. Two patients still had elevated levels five years and 14 years after total gastrectomy. One was discovered to have a parathyroid adenoma with hypercalcemia.

Total gastrectomy was curative in all the patients with the Zollinger-Ellison syndrome; lesser operations were not.

ESTABLISHING THE DIAGNOSIS OF THE Zollinger-Ellison syndrome may require exhaustive study of the patient over many years. A persistent ulcer diathesis and gastric hypersecretion are usually the first clues in the diagnosis.[1] Typically, patients have pronounced elevation of basal acid secretion. The ratio of basal acid output to maximum acid output (BAO:MAO) is usually greater than 65 percent.[2,3]

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Submitted April 12, 1971.

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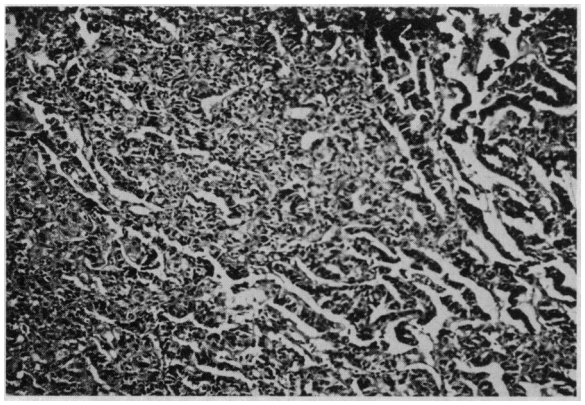

Figure 1.—Photomicrograph of liver nodule (Case 1) showing metastatic islet cell carcinoma. (Magnification X400. Hematoxylin-eosin stain.)

This report is based on data obtained from an extensive study of 13 patients with the Zollinger-Ellison syndrome. The patients were carefully followed by serial gastric secretory tests, by serum gastrin determinations, and, in two cases, by coeliac angiography. The case histories illustrate the difficulty in establishing the diagnosis by previously described methods and establish the value of serum gastrin determinations.

Reports of Cases

Case 1. A 43-year-old Caucasian man was seen for elective repair of an incisional hernia. Two years previously, he had had vagotomy and pyloroplasty for a bleeding duodenal ulcer. On biopsy at that time a nodule in the left lobe of the liver was thought to be a metastatic "papillary carcinoma." The postoperative course was complicated by infection and uremia requiring peritoneal dialysis and wound dehiscence. The biopsy slides (Figure 1) were reviewed and a diagnosis of metastatic islet cell carcinoma was made. Gastric secretory tests (Table 1, a) were within normal limits. A ventral hernia was repaired, the abdomen explored, and no tumor found. Ulcer symptoms continued and gastric secretory tests two years later showed decidedly elevated levels (Table 1, b). At operation there were large metastatic deposits within the liver and the region of the coeliac axis. A total gastrectomy* with Roux-en-Y esophagojejunostomy was done. The patient has done well and is working regularly as a machinist. His serum gastrin level, three years after total gastrectomy, was 3 picograms per ml.

*Total gastrectomy is 100 percent resection of stomach with histological evidence of circumferential esophageal mucosa at the proximal margin of the specimen and circumferential duodenal mucosa at the distal margin.

TABLE 1.—*Gastric Secretory Studies on 12 Patients with the Zollinger-Ellison Syndrome*

Case	*Anatomy**	*Acid Secretion mEq per hour* Basal	Maximum**	BAO:MAO***
1 a	V & P	3	47	.06
b	V & P	56	80	
2 c	Normal	4	15	
d	B II	23	27	.85
e	B I	9	11	
3 f	Normal	8	33	.24
g	B I	29	45	
4 h	B II	0.6	1.6	.38
i	B II	3	12	
5 J	Normal	80	72	1.11
k	V & P	61	81	
l	V & P	18	61	
m	V & P	63	76	
6 n	B II	16	17	.94
o	B II	4	23	
7 p	Normal	30	42	.71
8 q	Normal	26	56	.46
r	Normal	21	60	
9 s	Normal	13	14	.92
10 t	Normal	37	77	.48
11 u	B II	4.1	4.6	.90
13 v	Normal	14.7	17.7	.83
w	V & P	12	40	

*ANATOMY—V & P: Vagotomy and pyloroplasty. BI: Hemigastrectomy with gastroduodenostomy (Billroth I). B II: Hemigastrectomy with gastrojejunostomy (Billroth II).

**Maximum gastric acid secretion following intramuscular injection of betazole hydrochloride (Histalog®, Eli Lilly)—1.5 mg/Kg. body weight.

***Basal acid output:maximum acid output at time of diagnosis.

Case 2. A 50-year-old Negro man with a five-year history of duodenal ulcer and three previous episodes of bleeding requiring transfusion underwent emergency vagotomy and hemigastrectomy (Billroth II) in October, 1962. A gastric secretory study was normal (Table 1, c). The patient was well until 1965, when bleeding recurred. Basal gastric secretion was elevated (Table 1, d) and the Zollinger-Ellison syndrome was suspected. Despite extensive exploration, no tumor was found, and the previous anastomosis was converted to a gastroduodenostomy. He was well until October, 1968, when bleeding recurred. The serum gastrin level was found to be elevated (Table 2), establishing the diagnosis.

Case 3. A 45-year-old Negro man had intractable duodenal ulcer disease for 12 years. Gastric secretory levels were not extraordinary (Table 1, f). In September, 1965, vagotomy and

TABLE 2.—*Serum Gastrin Levels in 13 Patients with the Zollinger-Ellison Syndrome*

Case	*Anatomy*	*Postoperative Time Interval*	*Serum Gastrin Picograms/Ml*
1	Total gastrectomy	3 years	3
		5 years	5,000
2	Billroth I	4 months	600
3	Billroth I	3 years	7,000
	Total gastrectomy	2 months	3,333
4	Billroth II	3 months	550
5	Normal		2,000
	Total gastrectomy	7 months	87
6	98% gastrectomy	3 years	3,350
7	98% gastrectomy	3 years	2,000
8	Total gastrectomy	4 years	67
9	Total gastrectomy	14 months	4
10	Total gastrectomy	3 months	17
11	Billroth II	3 days	683
12	Total gastrectomy	14 years	6,600
	Preop parathyroid adenomectomy		8,000
	Parathyroid adenomectomy	1 week	10,000
13	Vagotomy and pyloroplasty	2 years	600

hemigastrectomy were done. A 5 mm pale yellow nodule on the right lobe of the liver was excised and diagnosed as a metastatic islet cell tumor (Figure 2). The pancreas and the duodenum were then carefully explored and no other tumors noted. The symptoms were relieved for a time but returned within a few months. Because of continued ulcer symptoms, the patient was readmitted in January, 1969. Serum gastrin levels were decidedly elevated (over 7,000 picograms per ml) as were the gastric acid levels (Table 1, g). At operation, a 7 cm tumor in the liver and a 4 cm tumor in the pancreas were found. Total gastrectomy with loop esophagojejunostomy and entero-enterostomy with intra-loop jejunal limb ligation was done.

Case 4. A 47-year-old Negro man was seen in September, 1965, with gastric retention from duodenal ulcer disease. On nasogastric tube drainage, the gastric output averaged three liters a day, with an acid concentration of 30 mEq per liter. A gastrin-secreting islet cell tumor was suspected and one was found embedded in the head of the pancreas. The tumor was removed and vagotomy and Billroth II resection were done. A postoperative acid study showed low levels (Table 1, h). The patient was admitted

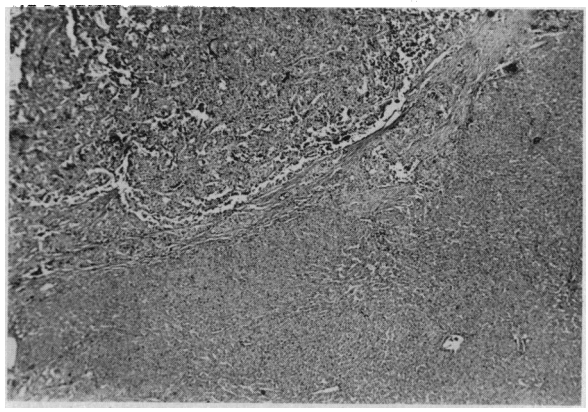

Figure 2.—Photomicrograph of liver nodule (Case 3) showing metastatic islet cell carcinoma. (Hematoxylin-eosin stain.)

again in November, 1968, because of melena. The acid secretion had increased (Table 1, i). The serum gastrin level was elevated to 550 picograms per ml. Total gastrectomy with Roux-en-Y esophagojejunostomy was done in March, 1969.

Case 5. A 36-year-old Caucasian man was referred with a diagnosis of multiple endocrine adenoma and with complaints of diarrhea, weight loss, nausea, and vomiting of three years' duration. Preoperative studies revealed elevated serum calcium (12.7 mg per 100 ml) and serum gastrin (2,000 picograms per ml) levels, a nonfunctioning thyroid nodule, and a maximum basal acid secretion of 111 mEq per hour with an average basal secretion of 80 mEq per hour (Table 1, j). At operation in March, 1966, "tumors of the pancreas" and a right adrenal adenoma were removed. On permanent section, the "pancreatic tumors" were identified as metastatic islet cell adenocarcinoma in lymph nodes. The acid secretion was unchanged by operation (Table 1, k). In April, 1966, the patient had right hemithyroidectomy and right inferior parathyroidectomy for adenomata. Basal acid secretion fell to 18 mEq per hour (Table 1, l) and the patient became asymptomatic. Diarrhea, nausea and vomiting recurred two and a half years later. Basal acid secretion had increased to 63 mEq per hour (Table 1, m). Total gastrectomy with Roux-en-Y esophagojejunostomy was done in September, 1968. The serum gastrin level was 87 picograms per ml five months after operation.

Case 6. A 53-year-old Negro man was seen first in November, 1952, with a three-day history

of pain and vomiting. In the next 18 months he was re-admitted four additional times for similar complaints. A duodenal ulcer niche was seen on several x-ray studies of the upper gastrointestinal tract. Antrectomy and vagotomy were done in June, 1954, for intractability and bleeding. During the next eight and a half years the patient was admitted to hospital 18 times for marginal or jejunal ulcers, bleeding, pain, and vomiting. He refused operation. Basal acid secretion was 18 mEq per hour. In January, 1965, an abdominal exploration for a pancreatic tumor was made but none was found. Five days following operation the patient had an emergency resection to control bleeding associated with gastritis. A 2 cm cuff of stomach was left on the esophagus to insure adequate anastomosis.

Since operation, the patient has had two episodes of bleeding. An ulcer in the gastric remnant was demonstrated in November, 1967. A pH electrode passed down the esophagus demonstrated acid-secreting (pH 1) mucosa. The patient refuses further operation. His serum gastrin level is 3,350 picograms per ml.

Case 7. A 43-year-old Caucasian man was admitted to hospital in 1964 with a four-year history of abdominal pain. An upper gastrointestinal series showed duodenitis and pancreatic calcifications. High basal acid levels (Table 1, p) suggested the diagnosis of the Zollinger-Ellison syndrome. The patient was readmitted eight months later because of pain, nausea, vomiting and diarrhea. In July, 1965, a near total gastrectomy was done after the diagnosis of a metastatic nodule on the liver was confirmed by biopsy. The patient continued to have epigastric pain and weight loss. A serum gastrin level obtained three years after operation was 2,000 picograms per ml. A pH electrode passed down the esophagus confirmed the presence of acid-secreting (pH 1) mucosa. The patient died of metastatic disease and cachexia four years after operation.

Case 8. A 38-year-old Negro man was first seen in December, 1961, with a three-year history of ulcer symptoms relieved by antacids. The basal secretory acid level was 2.6 mEq per hour. The patient was admitted for evaluation of hypercalcemia (11.5 to 13.8 mg per 100 ml). An upper gastrointestinal series showed a deformed duodenal bulb without ulceration. Bilateral inferior parathyroidectomy was carried out for a left inferior parathyroid adenoma. The patient was re-

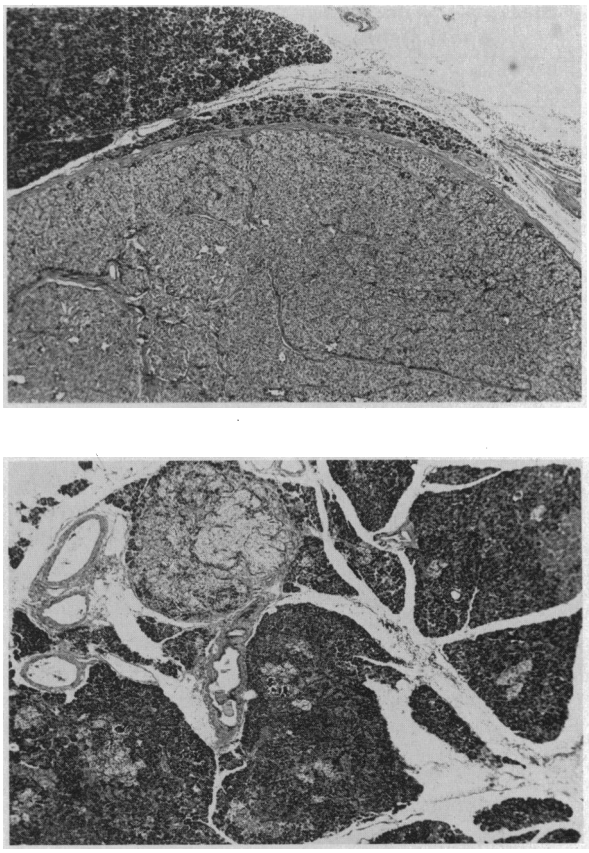

Figure 3.—Photomicrographs of pancreatic biopsy (Case 8) showing adenomatosis. (Magnification in upper frame, X25; in lower frame, X1000. Hematoxylin-eosin stain.)

admitted in April, 1965, with a history of melena and hematemesis, and found to have elevated acid levels (Table 1, q) and serum calcium levels (9.6 to 13 mg per 100 ml). A duodenal ulcer was visualized by x-ray studies. Partial pancreatectomy was carried out in May, 1965, for multiple adenomata (Figure 3). Postoperatively, acid levels remained elevated (Table 1, 4) and there was an episode of bleeding. A month later, total gastrectomy with esophagojejunostomy and entero-enterostomy was carried out. In October, 1969, the patient was discovered to have diabetes mellitus, easily controlled by diet and oral hypoglycemic agents. The serum gastrin level was 67 picograms per ml four years after total gastrectomy.

Case 9. A 65-year-old Caucasian woman with two-year history of epigastric pain, high BAO:MAO ratios (Table 1, s) and suspected Zollinger-Ellison syndrome, underwent operation for a posterior penetrating duodenal ulcer in March, 1969.

A 6 x 8 cm islet cell adenocarcinoma was found occupying the body and tail of the pancreas, and was removed by partial pancreatectomy. Total gastrectomy with Roux-en-Y esophagojejunostomy was performed at the same time. Postoperative pancreatic insufficiency was corrected by oral pancreatic enzyme supplementation. The serum gastrin level, 20 months after operation, was 4 picograms per ml. The patient gained 20 pounds in weight in the two years following operation.

Case 10. A 44-year-old Caucasian man with no previous history of ulcer disease underwent emergency operation for a perforated jejunal ulcer in August, 1968. An upper gastrointestinal x-ray series three months later revealed coarse mucosal folds in the duodenum, a deformed duodenal bulb, and evidence of retained secretions in the stomach. Gastric secretory studies were elevated (Table 1, t) but selective pancreatic arteriography was normal. Vagotomy and pyloroplasty were performed after thorough exploration of the abdomen, multiple biopsy and a partial pancreatectomy failed to reveal a tumor. The pancreas was nodular and firm but was normal on microscopic examination. Two months later, the patient returned with outlet obstruction and a gastric output of three liters daily with an acid concentration of 74 mEq per liter. After decompression, a large jejunal ulcer was seen on upper gastrointestinal series. Total gastrectomy with Roux-en-Y esophagojejunostomy was performed in February, 1969. No tumor was found. The stomach showed parietal cell hyperplasia. The serum gastrin level ten months after operation was 17 picograms per ml.

Case 11. A 38-year-old Caucasian woman with a one-month history of epigastric pain was discovered by x-ray studies to have gastric and duodenal ulcers. Multiple right renal stones and a large left renal stone were demonstrated by intravenous pyelography. A glucose tolerance test revealed diabetes mellitus. The ulcers healed with antacid therapy in one month. Four months later, in October, 1968, the patient had an emergency operation to close a perforated duodenal ulcer. In January, 1969, antrectomy, vagotomy and gastrojejunostomy were performed for bleeding gastritis. Bleeding recurred a month later, and an 80 percent gastrectomy was done. Exploration and biopsy of the pancreas revealed inflammatory changes only. The postoperative course was complicated by bleeding, fever, jaundice, and myocardial infarction. Gastric secretory studies, performed for the first time, revealed a basal level of 4 mEq per hour (Table 1, u). A serum gastrin level of 683 picograms per ml established the diagnosis of Zollinger-Ellison syndrome. Total gastrectomy with Roux-en-Y esophagojejunostomy was done in October, 1969. A large pancreatic islet cell tumor with hepatic metastasis was found. The patient was well seven months after the operation.

Case 12. A 48-year-old Caucasian man who had peptic ulcer disease since 1944 had gastric resection in 1950 for intractable duodenal ulcer. Three years later, total gastrectomy was done for bleeding recurrent ulcers. He had no ulcer symptoms thereafter. In 1965, the patient's brother was found to have the Zollinger-Ellison syndrome, which prompted evaluation of the entire family. It was discovered that three of four brothers and one of four sisters had the syndrome. The patient's daughter was discovered to have three parathyroid adenomas and a pancreatic adenoma. She had severe diarrhea but no symptoms of peptic ulcer disease. In October, 1967, the patient's serum gastrin level was 6,600 picograms per ml. In October, 1969, he developed symptoms of hypercalcemia. Two parathyroid adenomas were removed and the serum calcium level returned to normal. Serum gastrin levels, obtained preoperatively and postoperatively, were 8,000 and 10,000 picograms per ml respectively.

Case 13. A 14-year-old Negro boy was admitted for surgical correction of a duodenal ulcer that had been present for one year and had been refractory to intensive medical treatment. The patient's symptoms were epigastric pain, vomiting, and weight loss. An upper gastrointestinal series showed a duodenal ulcer niche with coarse gastric and duodenal mucosal folds. Gastric secretory studies (Table 1, v) showed a basal acid output of 14.7 mEq per hour and a maximum stimulated output of 17.7 mEq per hour. A diagnosis of Zollinger-Ellison syndrome was made. At laparotomy, a 4 cm islet cell adenocarcinoma was removed from the head of the pancreas. Two duodenal ulcers were found and vagotomy and pyloroplasty were done.

The patient then was well for eight months before epigastric pain recurred. The pain was mild and infrequent and was relieved by milk. The patient noticed black stools on two occa-

sions. An upper gastrointestinal series showed the effects of the pyloroplasty, but no prominent folds or ulcer niche were identified. Gastric secretory studies (Table 1, w) revealed a basal acid output of 12 mEq per hour and a maximum stimulated acid output of 40 mEq per hour. The serum gastrin level was over 600 pg per ml.

Discussion

The value of repeated gastric secretory studies in patients with recurrent peptic ulcer disease is evident in the cases here reported. The test is simple and readily available. It is reported that most patients with the Zollinger-Ellison syndrome will have BAO:MAO ratio of 65 percent or more.[2,3] A lower ratio, however, does not rule out the syndrome.[4] In this series of 13 patients, five had ratios of less than 50 percent at the time of diagnosis and two of the five had metastatic disease. In most patients the basal acid secretory levels will be continuously elevated. One of our patients (Case 4) was an exception. He had basal acid levels less than 5 mEq per hour consistently for four years. These levels were obtained after the patient had had a hemigastrectomy, but at a time when he was symptomatic from a marginal ulcer. He initially presented with outlet obstruction and a high gastric output. Acid levels at this time were 30 mEq per liter. This led to the correct diagnosis. The tumor was located in the head of the pancreas at celiotomy. This illustrates the importance of serial gastric analysis for patients presenting with complications of duodenal ulcer disease.

Two patients (Cases 1 and 3) were diagnosed by biopsy of small "incidental" tumor nodules on the liver at operation for duodenal ulcer. In these patients results of secretory studies were normal and there were no historical data suggesting the Zollinger-Ellison syndrome. One patient had a mistaken diagnosis of "papillary carcinoma" when the islet cell origin of the biopsy specimen was not recognized. He later presented for elective ventral hernia repair. After review of the biopsy slides, the abdomen was thoroughly explored at incisional herniorrhaphy. Additional tumor was not found. The patient continued with symptoms of duodenal ulcer and finally showed elevated acid levels. The other patient underwent operation for intractable duodenal ulcer disease. A 5 mm nodule was removed from the liver and it proved to be metastatic islet cell adenocarcinoma. Three years later, the secretory studies became characteristically elevated.

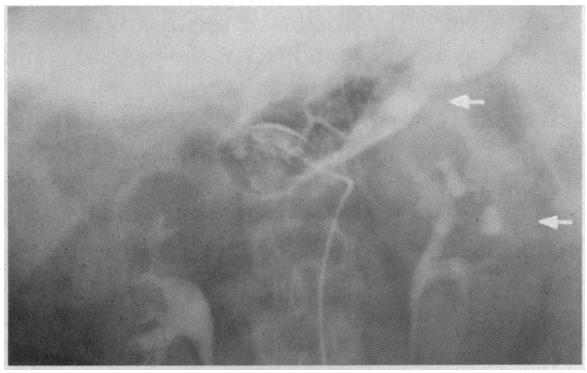

Figure 4.—Celiac arteriogram demonstrating metastatic islet cell tumor in the celiac axis (upper arrow) and jejunal mesentery (lower arrow) confirmed by laparotomy.

The period between fortuitous discovery of tumor and onset of hypersecretion was two and a half years in three patients. Symptoms recurred in one patient (Case 5) after removal of multiple adenomata including metastatic islet cell tumors to peripancreatic lymph nodes. Operation revealed metastatic deposits in the coeliac axis and jejunal mesentery which had been demonstrated preoperatively by coeliac angiography (Figure 4). Hypersecretion was noted two and a half years after incidental discovery of tumor in the other two patients (Cases 1 and 3).

Two patients (Cases 5 and 8) presented with multiple adenomata and hyperparathyroidism. The combination of hypercalcemia and peptic ulcer disease suggests multiple endocrine adenomata.[5] The patients had serum calcium levels of 12.7 and 13.8 mg per 100 ml, and both had history of duodenal ulcer disease. One had a basal acid output of 111 mEq per hour and adenomata in the pancreas, adrenal, thyroid and parathyroid glands. The other had normal secretory studies and a functioning parathyroid adenoma. Three years later, the latter had basal acid output of 26 mEq per hour, and multiple adenomata were found in the pancreas. Only by repeated secretory studies was the correct diagnosis reached. Patients with hypercalcemia and peptic ulcer disease should have serum gastrin determinations.

Serum gastrin levels, measured by a radioimmunoassay technique, were determined in all

patients (Table 2).* In contrast to gastric secretory studies, serum gastrin levels were elevated in all patients before total gastrectomy. Gastrin levels may be diagnostic at a time when acid studies are normal (Cases 1 and 3). The test should be performed on all patients suspected of having this syndrome.

A drop in the serum gastrin level was noted in six patients following total gastrectomy. Two patients (Cases 6 and 7) who had near-total gastrectomy, as well as all other patients undergoing less than total gastrectomy, continued to have diagnostically elevated serum gastrin levels and clinically evident disease.

Two patients (Cases 1 and 12) with total gastrectomy had elevated serum gastrin levels five years and 14 years after the operation. Both patients were asymptomatic. The second patient was found to have a parathyroid adenoma with hypercalcemia. The serum gastrin remained elevated following removal of the adenoma and return to normal serum calcium levels.

Total gastrectomy was curative in all cases. None of these patients was cured of the disease by a lesser operation. As long as acid-producing parietal cells and gastrin-producing tumor cells are present, the disease continues. Frozen section documentation of total gastrectomy at celiotomy is imperative.

*The serum gastrin determinations were performed by Dr. James E. McGuigan (Cases 4 to 10) and Dr. Rosalyn Yalow (Cases 1 to 3, 11 to 13).

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