A Gastric Factor in the Pathogenesis of the Zollinger-Ellison Syndrome

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IT WAS RECENTLY suggested that the stomach in some way influences the growth of islet cells in the Zollinger-Ellison syndrome.[12] This suggestion was based on observations that at the time of exploratory reoperations in two patients no further progression of metastases and the absence of metastases were found 4 and 5 years after total gastrectomy for metastatic "ulcerogenic tumors" of the pancreatic islets. Further evidence now is presented to indicate that total gastrectomy in this syndrome can lead to visible regression of metastatic islet cell tumor. This observation is pertinent to the mechanism of the still unknown pathogenesis of the Zollinger-Ellison syndrome and in the operative management of patients with this condition.

The association of non-Beta islet cell adenoma with gastric hypersecretion of acid and fulminating ulcer disease was clearly described in 1955 as a definite clinical entity,[35] later called the Zollinger-Ellison syndrome. The "ulcerogenic" potential of the islet cell tumor or its metastases was put on firm physiologic basis by the finding of gastrin-like activity in tissue extractions and assays using denervated gastric fundal pouches.[14] That the humoral substance is indeed gastrin was further determined.[15] The finding of gastrin activity in metastases,[2, 10, 17] the description of metastases without demonstrable primary pancreatic lesions, the finding of multicentric tumors or islet cell hyperplasia or microadenomatosis led to a concept of total gastrectomy as the treatment of choice by some surgeons rather than excision of the tumor.[11, 36] Furthermore, the clinical observation that any method other than total gastrectomy, that is, vagotomy and subtotal gastrectomy, failed to eliminate the severe ulcer potential in many of these patients added to the concept of treatment by complete excision of the so-called "end organ," the stomach.[11] Moreover, it has been noted that any procedure other than total gastrectomy usually was followed by progressive metastatic disease when the ulcer disease was not immediately fatal; that total gastrectomy would control the ulcer diathesis was obvious but that this operation might affect islet cell tumor growth was realized only over a period of time during which known metastases seemed to stop growing or could not be found at second look operations (patients W. M. and L. R.).[12] Therefore the relationship of the stomach to islet cell tumors was studied in subsequent patients. The pertinent findings in 11 patients who have had definitive operations for the Zollinger-Ellison syndrome at the University of Kansas Medical Center are listed in Table 1. The first six cases in Table 1 have been reported previously[12] but are included here for reference to the gastric-islet cell hypothesis. Two patients are presented in detail to illustrate (a) the per-

Presented before the American Surgical Association, April 17–19, 1968, Boston, Massachusetts.

These investigations were supported in part by NIH Grant #FR-67.

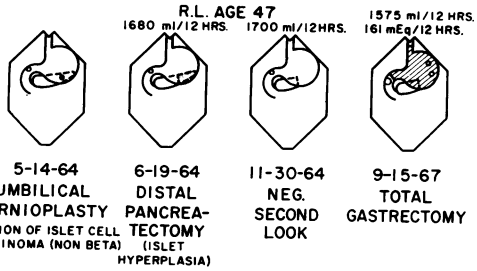

FIG. 1. Diagrams of findings at operations in patient R. L. (No. 7 in Table) which illustrate persistence of islet cell hyperplasia and continuation of the Zollinger-Ellison syndrome after excision of solitary non-Beta islet cell carcinoma until the time of total gastrectomy.

sistence of the syndrome (and the associated islet cell hyperplasia) after complete excision of a solitary primary islet cell carcinoma until the time of total gastrectomy (patient R. L.) and (b) the visible regression of islet cell carcinoma metastases following total gastrectomy (patient C. P.).

Illustrative Cases

R. L. (No. 7 in Table) (Fig. 1), a 47-year-old man with a family history of diabetes (both parents and five of nine siblings) gave a history, with x-ray evidence, of duodenal ulcer since 1954. In May 1964, during operation for umbilical hernia, a 2cm nodule was removed from the anterior surface of the body of the pancreas. The microscopic report indicated this nodule to be adenocarcinoma of the pancreas, showing anaplastic hyperchromatic cells with frequent mitotic figures invading widely into stroma. X-ray series showed a duodenal ulcer. The patient was referred to the University of Kansas Medical Center where a distal pancreatectomy with splenectomy, including the site of the prior excision of the malignant pancreatic nodule, disclosed no obvious pancreatic tumor or metastatic disease. Microscopic examination of the body and tail of the pancreas revealed large (twice normal), very prominent and well-demarcated islets of Langerhans without malignant change. Because a preoperative glucose tolerance test indicated mild diabetes, he was given oral insulin, a diabetic diet, frequent feedings and antiacids, and was dismissed from the hospital to return for further studies. In November, 1964 he was readmitted, having lost 65 pounds; his ulcer appeared to be easily controlled symptomatically by medical mangement. An aortic angiogram revealed no evidence of a pancreatic tumor and a hepatic scan showed no evidence of metastases. A 12-hour gastric aspiration was 1700 ml.; acid concentration values are not recorded. An abdominal exploratory reoperation showed no evidence of metastatic tumor in pancreatic, duodenal or celiac lymph nodes or in the liver. Because of the history of weight loss and of good medical control of the ulcer diathesis, no operative procedure for ulcer was done. The patient was continued on chemotherapy for ulcer and diabetes and subsequently gained weight and felt well. In 1967 symptoms of ulcer increased in severity with epigastric and right upper quadrant abdominal pain, nausea and vomiting. The diabetes now required parenteral insulin. A 12-hour gastric aspirate yielded 1,550 ml. containing 102 mEq. free HCl per liter and 136 mEq. per liter on Histalog stimulation (basal to maximal concentration ratio of 0.75). A serum gastrin assay at that time was reported as negative. X-rays showed gastric hyperrugation and a large postbulbar duodenal ulcer without obstruction. Serum calcium and phosphorus were normal. Glucose tolerance tests were markedly diabetic. Hepatic scan and sella turcica x-rays were normal. Review of the original microscopic slide of the pancreatic tumor confirmed the islet cell carcinoma. At operation the ulcer of the second portion of the duodenum had perforated and sealed to the under surface of the liver. The stomach appeared hypertrophied and the head of the pancreas was slightly thickened. Because of the fulminating course of the ulcer disease at this time, and because of failure of control by either the excision of the primary carcinoma or the distal hemipancreatectomy of islet cell hyperplasia, a total gastrectomy with esophagojejunostomy en Roux Y was done. The patient has been well since that time and there has been a remarkable improvement in glucose tolerance. There are high levels of serum insulin and normal levels of growth hormone.[1]

C. P. (No. 8 in Table) (Fig. 2), a 43-year-old man had a history of renal stones from 1953. He has had symptoms and x-ray confirmation of a duodenal ulcer since 1959. In September 1960, he was told that he was diabetic and had hypertension. In December 1960, because of findings indicative of hyperparathyroidism, his surgeon excised a left parathyroid gland which was histologically hyperplastic, and a thyroid nodule, histologically normal. He continued to complain of lethargy, weakness, nocturia and polyuria. In November 1962, he was referred to the University of Kansas Medical Center with the primary complaint of increasing epigastric pain and bloating, relieved by milk and antacids. The family history indicated that the mother had a "stomach ulcer." Physical examination revealed a lethargic patient with no abnormalities except blood pressure of 150/105,

mild epigastric tenderness and a healed cervical scar. The laboratory data are listed in Table 1. Upper gastrointestinal x-rays demonstrated a duodenal ulcer with deformity. A diagnosis of polyglandular syndrome was made and on December 6, 1962 an exploration of the neck with left thyroid lobectomy failed to uncover the suspected adenoma of the parathyroid. Twelve days later the neck and mediastinum was reexplored with excision of a parathyroid adenoma (1.6 cm. in diameter) posterior to the inferior pole of the right thyroid lobe. Following this, the serum calcium and phosphorus gradually returned to normal. Postoperative psychosis and one episode of upper gastrointestinal hemorrhage reduced the hemoglobin to 8 Gm./100 ml. After a prolonged hospital course he was dismissed and prescribed a medical regimen including vitamin D, calcium lactate, antacids and a low salt diet. The patient was seen from time to time in the Endocrine Clinic without evidence of abnormal parathyroid function but complained of upper abdominal pain, radiating to the back. In August 1967 a "routine" chest x-ray revealed a circular mass in the right lung field approximately 4 cm. in diameter and a smaller one on the left, posterior to the heart (Fig. 6). He was readmitted to the hospital for evaluation. The blood pressure was 130/70 at this time. Hemoglobin was 5.1 Gm./100 ml. Serum electrolytes were normal including calcium of 4.3 mEq./l, phosphorus of 2.7 mEq./l. Several gastric secretion tests were variable but one, the highest, 12-hour gastric volume measured 1,350 ml. containing 92 mEq. free HCl per liter (124 mEq./12 hr.). Histalog stimulation increased the concentration to 104 mEq./l. (BAC/MAC ratio of 0.9). Glucose tolerance was normal but serum insulin levels were high, as were growth hormone levels which were suppressed by glucose. A serum gastrin assay drawn at this time was reported as negative. X-ray examinations demonstrated bilateral pulmonary metastases, a normal sella turcica, normal long bones, nephrocalcinosis and renal stones, gastric hyperrugation, flocculation of the small intestine, a large postbulbar duodenal ulcer with nodularity of the duodenum. A hepatic scan was consistent with multiple liver metastases (Fig. 8). A diagnosis of polyglandular Zollinger-Ellison syndrome with hepatic and pulmonary metastases was made. The patient was given several transfusions of whole blood and on September 22, 1967, operation revealed a 4 cm. mass in the tail of the pancreas with several smaller masses in the body and head of the pancreas, multiple small liver metastases, a thickened stomach and a large ulcer of the second portion of the duodenum. A frozen section microscopic examination of one liver metastasis was consistent with islet cell carcinoma. The

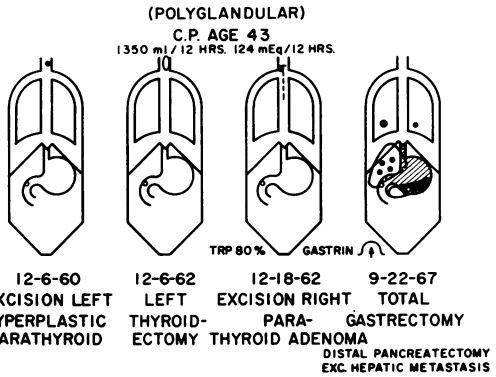

FIG. 2. Diagrams of findings at operations in patient C. P. (No. 8 in Table) which illustrate persistence of the Zollinger-Ellison syndrome after excision of an adenoma and hyperplasia of the parathyroid glands until the time of total gastrectomy and excision of one of the primary non-Beta islet cell carcinomata. The pulmonary and histologically proven liver metastases visibly regressed shortly after the last operation. Gastrin assay of the tumor was positive.

tail of the pancreas containing the larger mass (islet cell carcinoma on frozen section) and the spleen were removed and a total gastrectomy with esophagojejunostomy en Roux Y and appendectomy were done. Multiple nodules in the remaining pancreas and the liver were left in the patient. Microscopic examination of the tissues revealed non-Beta islet cell carcinoma of the tail of the pancreas (Fig. 3) (one section reveals a small clump of Beta islet cells in the midst of a large mass of non-Beta islet cell carcinoma). There were no metastases to lymph nodes but there were small islet cell carcinomata at the line of pancreatic excision (Fig. 4), hepatic metastases (Fig. 5), chronic peptic ulcer of the duodenum, gastric mucosal hyperplasia, with ectopic pancreatic tissue in the wall of the stomach. Tissue assay for gastrin was positive.[15] Assay of the tumor for insulin was positive.[16]

Postoperative course was uncomplicated and follow-up study continued in the surgical clinic. A chest x-ray 46 days after operation demonstrated remarkable reduction in the size of the pulmonary metastases. At 66 days the lesions are described as "very small," and at 82 days they are not discernible (Fig. 6). Planigraphic studies show two opacities on the right and one on the left, each less than 1 cm. in diameter at 82 days (Fig. 7), with residual shadows at 115, 144 and 192 days. Hepatic scans at 67 days and 82 days are reported as normal, without evidence of metastatic disease (Fig. 8). The patient is well, with normal fasting blood sugar values but with decreased glucose

TABLE 1. *Clinical Features of Eleven Patients with Zollinger-Ellison Syndrome**

No.	Pt.	Age & Sex	Acid Secretion: 12-hour volume	mEq./L.	mEq./12-hr.	BAC/MAC	Hist. D.U. (yrs.)	Year	Findings	Operations	Gastrin Assays: Ser.	Gastrin Assays: Tis.	Associated Findings	Result
1	A. H.	54 M					14	1937	Duodenal ulcer					
								1950	Perforated duodenal ulcer	Surgical closure			Sinus bradycardia	
			1800	96	173	0.8		1951	Duodenal ulcer Islet cell carcinoma in tail of pancreas	Subtotal gastrectomy Distal pancreatectomy			Blood type A neg. Fasting blood sugar 59–63 mgm. %	
								1952	Stomal ulcer, perforated	Vagotomy, partial gastrectomy			Normal chest x-ray	
			900	78	71			1954	Stomal ulcer Liver metastases	Partial gastrectomy				
								1957	Stomal ulcer Liver metastases					Death 1957 Pulm. embolism Stomal ulcer Liver metastases
2	G. P.	74 M					8	1954	Duodenal ulcer	Gastrojejunostomy			Blood type O pos.	
			2800	76	213	3.8		1962	Stomal ulcer Islet cell carcinoma of pancreas with diffuse metastases	Laparotomy with biopsy only	0		Diarrhea Calcium 4.3 mEq./l. Phos. 2.7 mEq./l. Normal chest x-ray Normal sella B-12 uptake 12%	Death 1962 Pulm. embolism Stomal ulcers Diffuse metast. Also Ca of stomach & normal pituitary at autopsy
3	J. B.	41 M					4	1956	Duodenal ulcer				Blood type 0 pos.	
			2800	120	336			1960	Duodenal ulcer 3rd portion Esophageal ulcer Islet cell Ca of pancreas with metastases to nodes, liver, supraclavicular nodes	Vagotomy & subtotal gastrectomy	+		Diarrhea; normal sella, normal chest x-rays; increased alpha & gamma globulin; sickling of rbc's; calcium 4.5 mEq./l. phos. 1.9 mEq./l.	
			2000	110	220			1961	Stomal ulcer	Gastric irradiation				
								1963	Stomal ulcer, diffuse metastases					Death 1963 Hemorrhage, generalized metastases pituitary adenoma

* The patients have been studied whenever possible for gastric secretory function (12-hour overnight collection, basal and maximal Histalog—stimulated acid concentration) (BAC/MAC refers to the ratio of the basal to the maximal acid concentration), islet cell function (acid and alkaline oral glucose tolerance tests, intravenous glucose tolerance tests, serum assays for immuno-reactive insulin), serum assays for human growth hormone, serum and tissue assays for gastrin, immune-antibody localization for gastrin, blood type, associated endocrine abnormalities, and the clinical course of the disease from both the ulcer and the tumor aspects. Patient A. H. was operated upon by Dr. T. G. Orr, Sr., patient D. G. by Drs. Don R. Miller and F. F. Allbritten, patient R. M. by Dr. C. Hardin and patient M. S. by Dr. Don Miller. The adrenalectomy in patient L. R. was done by Dr. C. F. Kittle and the excision of the parathyroid adenoma in patient C. P. was done by Dr. A. Heilbrunn. The assays for immuno-reactive insulin and human growth hormone were done by Dr. R. Bolinger. The immuno-antibody localization of gastrin in tumor and tissue insulin assay were done by Dr. M. Greider, St. Louis, Mo. The serum assays for gastrin were done by Dr. S. Wilson, Milwaukee, Wisc., and by Dr. G. Endahl, Columbus, Ohio. The tissue assays for gastrin were done by Professor R. Gregory, Liverpool, England and by Dr. C. Code, Rochester, Minn. The measurement of islet changes in the pancreas in experimental dogs was done by Dr. John Nichols. The assistance of all is gratefully acknowledged.

TABLE 1. (*Cont.*)

No.	Pt.	Age & Sex	Acid Secretion: 12-hour volume	Acid Secretion: mEq./L.	Acid Secretion: mEq./12-hr.	Acid Secretion: BAC/MAC	Hist. D.U. (yrs.)	Year	Findings	Operations	Gastrin Assays: Ser.	Gastrin Assays: Tis.	Associated Findings	Result
4	E. E.	49 M					25	1937	Duodenal ulcer				Blood type O pos.	
								1957	Perforated duodenal ulcer	Surgical closure			Diarrhea	
				68		0.7		1961	Duodenal ulcer				Secretin test-decreased bicarbonate excretion	
			4560	108	492	1.1		1962	Perforated jejunal ulcer Diffuse islet cell hyperplasia	Total gastrectomy, partial jejunectomy, distal pancreatectomy			Normal insulin tolerance, normal fasting glucose, polyuria, normal sella & chest; Calcium 5.1 mEq./l. Phosphorus 2.7 mEq./l.	
													Alcoholic	
								1967	Well		0		Clubbing of fingers	Well until accidental death 1967
5	W. M.	14 F					0	1961	Perforated jejunal ulcer	Surgical closure			Diarrhea	
			1700	118	201	0.7		1962	Jejunal ulcers Metastatic islet cell carcinoma in pancreatic lymph nodes	Total gastrectomy, partial jejunectomy, excision of node		+	Blood type A pos. Calcium 4.3 mEq./l. Phosphorus 2.4 mEq./l. Normal sella, normal visual fields; 17-K.S. 16.3 mgm./24 hrs 17-KGS 19.1 mgm./24 hrs P.B.I. 4.1 mcg. %	
								1966	No disease found	Second look			Delayed menses FSH > 100 m.u.	
								1967			0		(ovarian failure)	
								1968			0		Normal liver scan Reactive glucose tolerance Elevated growth hormone	Well 1968—No evidence of recurrence
6	L. R.	36 M					6	1950	Lipomata	Excision				
								1955	Duodenal ulcer Cushing's syndrome Right adrenocortical adenoma	Right adrenalectomy			Blood type O neg. Diarrhea Normal sella Calcium 5.4 mEq./l. Phosph. 1.5 mEq./l. 17 K.S. 11.7 mgm. P.B.I. 3.9 mcg.%	

TABLE 1. (*Cont.*)

No.	Pt.	Age & Sex	Acid Secretion: 12-hour volume	mEq./L.	mEq./12-hr.	BAC/MAC	Hist. D.U. (yrs.)	Year	Findings	Operations	Gastrin Assays: Ser.	Gastrin Assays: Tis.	Associated Findings	Result
		90						1957	Duodenal ulcer				Normal glucose tolerance	
			3000	120	360	0.8		1961	Duodenal ulcer, 2nd portion, metastatic islet cell pancreatic carcinoma in lymph nodes, duodenum, liver, lung	Total gastrectomy and excision of a node and a liver metastasis		0	Steatorrhea Fecal fat 31.3%	
								1961	Pulmonary metastasis (rt.)	Excision of pulmonary metastasis		0	Decreased glucose tolerance Reactive curve 17-K.S. 11.9 mgm./24 hrs.	
								1966	No abdominal disease Mediastinal node metastases	Second look, abdominal & thoracic; excision of mediastinal metastases		0 0	Normal liver scan Normal sella Normal visual fields	
								1967	Lipomatosis	Excision biopsy	0		Normal liver scan Normal chest x-ray	
								1968					*Decreased glucose tolerance, normal liver scan, normal sella, normal chest x-ray *(delayed elevation Growth hormone)	Well 1968—No evidence of recurrence
7	R. L.	47 M					10	1954	Duodenal ulcer					
								1964	Duodenal ulcer; 2 cm. islet cell carcinoma on surface of pancreas Lymph node normal	Excision of islet cell carcinoma during umbilical hernioplasty			Blood type B pos. Decreased glucose tolerance; strong family history of diabetes	
			1680					1964	Duodenal ulcer; islet cell hyperplasia	Distal pancreatectomy with splenectomy			Decreased glucose tolerance	
			1700					1964	Duodenal ulcer (mild) No tumor found	Second look			Normal aortogram, liver scan, sella, & chest	
			1575	102	161	0.8		1967	Large duodenal ulcer, 2nd portion; no tumor found	Total gastrectomy	0		Marked decreased glucose tolerance Calcium 4.7 mEq./l. Phosph. 1.5 mEq./l.	

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No.	Pt.	Age & Sex	Acid Secretion: 12-hour volume	Acid Secretion: mEq./L.	Acid Secretion: mEq./12-hr.	Acid Secretion: BAC/MAC	Acid Secretion: Hist. D.U. (yrs.)	Year	Findings	Operations	Gastrin Assays: Ser.	Gastrin Assays: Tis.	Associated Findings	Result
								1968					Normal liver scan Marked improvement in glucose tolerance Normal growth hormone; high insulin	Well; no evidence of recurrence
8	C. P.	43 M					3	1953	Renal stones					
								1959	Duodenal ulcer				"Diabetes" "Hypertension"	
								1960	Duodenal ulcer Hyperparathyroidism Parathyroid hyperplasia Thyroid nodule, normal	Excision left parathyroid gland; excision thyroid nodule			Calcium 6.5 mEq./l. Phosph. 2.35 mgm. % PBI 2.4 mcg. % 2-hr. p.p. blood sugar 150 mgm %. Normal sella & chest Nephrocalcinosis	
								1962	Duodenal ulcer Continued hyperparathyroidism	Left thyroidectomy			Blood type A pos.	
			1300	84	109	0.7		1962	Continuing hyperparathyroidism	Excision rt. parathyroid adenoma, sternal split			Calcium 7.4 mEq./l. Phosph. 1.0 mEq./l. TRP 80% Normal sella, chest, hands BP 150/105; hgb. 13.5 gm. % 17-K.S. 19.7 mgm./24 hrs. 17-K.G.S. 30.3 mgm./24 hrs. Decreased glucose tolerance with reactive curve Elevated growth hormone suppressed by glucose PBI 3.1 mcg. % 5-OH.I.A.A. negative	
			1350	92	124	0.9		1967	No hyperparathyroidism Duodenal ulcer 2nd portion; duodenal nodularity; multiple islet cell carcinomata of pancreas with metastases to liver and lungs	Total gastrectomy Excision of tumor in tail of pancreas Excision of hepatic metastasis	0	+	Pulmonary metastases, bilateral; hepatic scan, multiple metastases; normal sella Calcium 4.3 mEq./l. Phosph. 2.7 mEq./l.	

TABLE 1. (*Cont.*)

No.	Pt.	Age & Sex	Acid Secretion: 12-hour volume	mEq./L.	mEq./12-hr.	BAC/MAC	Hist. D.U. (yrs.)	Year	Findings	Operations	Gastrin Assays: Ser.	Gastrin Assays: Tis.	Associated Findings	Result
													BP 130/70 hgb. 5.1 gm. % 17-K.S. 12.8 suppressed to 5.2 mgm./24 hrs. 17-K.G.S. 13.8 suppressed to 4.1 mgm./24 hrs. Normal glucose tolerance; 5-OH.I.A.A. negative; PBI 4.4 Insulin assay positive.	
								1968	Regression of pulmonary and hepatic metastases		0		Normal chest x-rays at 82 days; residuum on planigram, 82–192 d. Normal hepatic scan at 67 days; marked decreased glucose tolerance; elevated growth hormone without suppression by glucose Positive insulin assay	Well with no evidence of recurrence.
9	D. G.	43 M					5	1960	Duodenal ulcer					
								1963	Diabetes					
								1964	Exacerbation duodenal ulcer					
								1965	Perforating duodenal ulcer					
								1965	Perforated jejuno-colic fistula; fat necrosis	Colostomy Gastrostomy			Diarrhea Fasting blood sugar 259 mgm. % Free peritoneal air Blood type A neg.	
			1200	130	156			1965	Jejunal ulcers; large islet cell carcinoma body of pancreas with tumor thrombosis of splenic vein; elevated alkaline phosphatase (liver not described)	Subtotal pancreatectomy; total gastrectomy Closure of colostomy			Normal chest x-ray Calcium 4.2 mEq./l. Phosph. 2.5 mEq./l. Alkaline phosphatase 3.9 B.L. units	

TABLE 1. (*Cont.*)

No.	Pt.	Age & Sex	Acid Secretion: 12-hour volume	Acid Secretion: mEq./L.	Acid Secretion: mEq./12-hr.	Acid Secretion: BAC/MAC	Hist. D.U. (yrs.)	Year	Findings	Operations	Gastrin Assays: Ser.	Gastrin Assays: Tis.	Associated Findings	Result
								1966	Esophageal stricture	Esophageal dilatation				
								1968	Afferent loop obstruction; islet cell tumor pancreas and liver	Duodeno-jejunostomy, jejunojejunostomy; biopsy of liver	0		Normal chest x-ray Liver scan metastases probable; alkaline phosphatase 4.4 B.L. units; fasting blood sugar 120 mgm. %; B-12 less than 2% absorption	Patient well with tumor and is being studied
10	R. M.	42 M	1800	102	184	0.8	3	1960	Perforated duodenal ulcer	Surgical closure				
								1963	Duodenal ulcer	Vagotomy and antrectomy with gastrojejunostomy			Blood type O pos. Gastric hyperrugation Normal chest	
								1963	Stomal ulcer	Subtotal gastrectomy Biopsy of pancreas			Diarrhea Calcium 4.5 mEq./l. Phosph. 1.7 mEq./l.	
								1966	Stomal ulcer				PBI 5.2 mcg. %	
								1968	Stomal ulcer	Total gastrectomy			Decreased glucose tolerance; B-12 11% Calcium 4.3 mEq./l. Phosph. 1.8 mEq./l.	Well without evidence of tumor
11	M. S.	45 F					12	1948	Duodenal ulcer					
								1949	Perforated duodenal ulcer	Surgical Closure			Blood type A pos.	
			750					1950	Duodenal ulcer	Subtotal gastrectomy (3/4)				
								1952	Stomal ulcer					
								1960	Stomal ulcer	Vagotomy & partial gastrectomy				
								1965	Esophageal stricture	Eight esophageal dilatations				
								1967	Large stomal ulcer and long esophageal stricture	Total gastrectomy and thoracic esophagectomy			Hemoglobin 3.5 gm. % Fasting blood sugar 91 mgm. % Calcium 4.5 mEq./l. Phosph. 2.2 mEq./l. Normal chest	Well without evidence of tumor

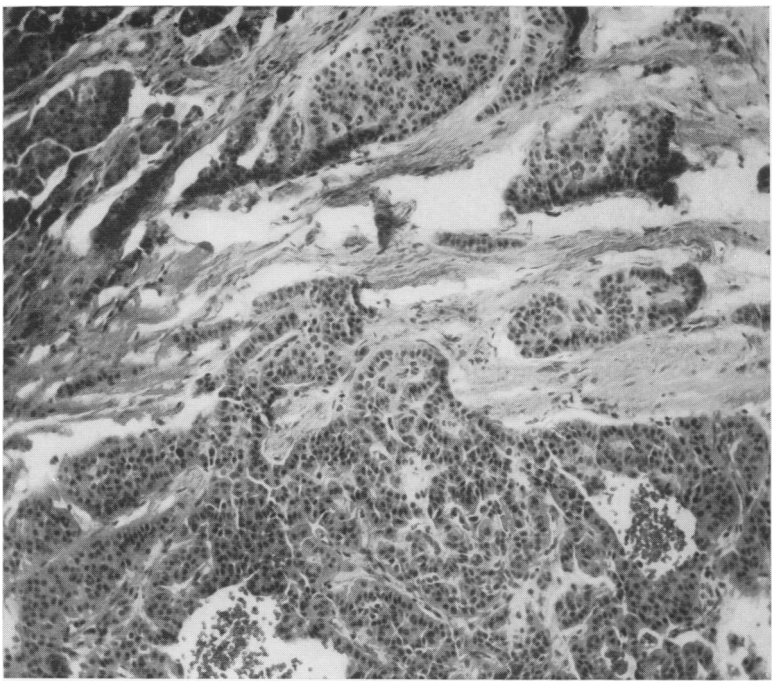

FIG. 3. Photomicrograph of one of the primary islet cell carcinomata of the pancreas from patient C. P. Cords of non-Beta islet cells lined by capillaries show invasion of stroma; there are cellular pleomorphism and mitoses. Original magnification × 137.

tolerance, normal to high growth hormone levels not suppressed by glucose, and is continuing follow-up examinations.

Observations

Table 1 lists significant findings observed in 11 patients who had the clinical features of the Zollinger-Ellison syndrome. Nine had histologically proven islet cell abnormalities; in one (R. M.) a pancreatic biopsy was inadequate for reliable identification of islet cell changes and in the other (M. S.) a pancreatic biopsy was not done. All of the islet cell abnormalities histologically were non-Beta in type and eight of the nine were described as malignant. Marked hypersecretion of acid with a high ratio of basal acid concentration to maximal acid concentration, described by Ruppert *et al.*[28] as diagnostic if over 0.6, was present in all who were tested: in one patient (M. S.), a severe esophagitis stricture (3 mm. lumen) prevented testing when seen at the University of Kansas Medical Center. Nine of the 11 patients were males. The ages ranged from 14 to 74 years.

Evidence of a Gastric Factor

Investigations in these 11 patients and from the literature lead to evidence which supports a hypothesis that a gastric factor or gastric acid hypersecretion is an important mechanism in the pathogenesis of the Zollinger-Ellison syndrome and that islet cell changes are manifestations secondary to a gastric influence, rather than vice versa as has been supposed. The evidence includes:

1. Regression of metastatic islet cell carcinoma in the lungs and liver observed radiologically shortly after total gastrectomy in patient C. P.

2. Absence of metastases at exploratory reoperation in patient W. M., 4 years after total gastrectomy for metastatic islet cell carcinoma.

3. Absence of hepatic and lymph node metastases and the finding of "dormant" or apparent lack of progression of mediastinal lymph node metastases (excised) at exploratory reoperation in patient L. R., 5 years after total gastrectomy for histologi-

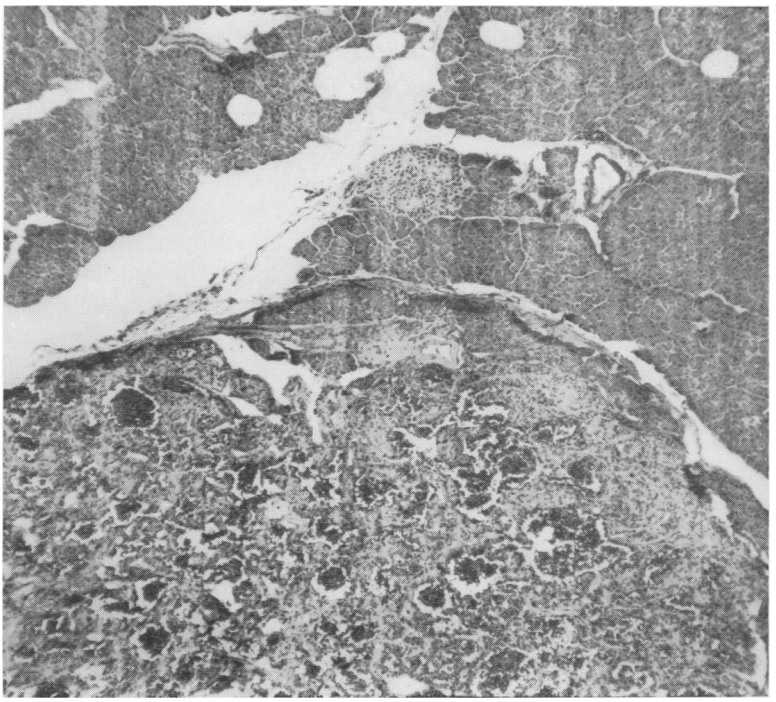

FIG. 4. Photomicrograph of one of the islet cell carcinomata in the pancreas found at the line of excision of the distal pancreatectomy in patient C. P. Original magnification × 66.

cally proven hepatic, pancreatic lymph node and pulmonary metastases. This patient had had massive gastric hypersecretion of acid despite the fact that no gastrin activity by assay was found in metastases to pancreatic lymph nodes, lung, or mediastinal lymph nodes on three difference occasions in two different laboratories.

4. Failure of complete excision of a solitary islet cell carcinoma in patient R. L. to alter the associated islet cell hyperplasia or to prevent continuation of the syndrome which, when fulminating, finally was arrested by total gastrectomy.

5. Failure of operations short of total gastrectomy to prevent the diffuse spread and progression of metastases, ulcer complications and death in three patients with known metastases (A. H., G. P. and J. B.). Tissue assays for gastrin were done in two (G. P. and J. B.) and was positive in one (J. B.).

6. Four patients (W. M., L. R., R. L. and C. P.) who had total gastrectomy for islet cell carcinoma are well, without evidence of progressive metastases up to 7 years. Two of three of these patients (W. M. and C. P.) had positive tissue assays for gastrin at total gastrectomy. At present, these four patients have negative serum assays for gastrin activity. A fifth patient (D. G.) who had total gastrectomy and distal pancreatectomy for extensive islet cell carcinoma of the pancreas 2½ years ago has evidence of persistent islet cell tumor of the pancreas and liver without distant spread. Total gastrectomy in this patient, as in the others, appears to be complete in that no gastric mucosa is seen on biopsy of the esophagojejunostomy, the pH at that site remains alkaline on histamine stimulation and a cobalt-tagged B-12 Shilling test indicates less than two per cent absorption. A serum assay for gastrin is negative. This patient is being investigated for pituitary or other endocrine influences, though none are clinically evident at this time.

7. A history of duodenal ulcer with radiologic or operative confirmation three to

25 years prior to the development of the fulminating course was present in 10 of the 11 patients; the illness of only one patient (W. M.) began with a perforated jejunal ulcer without a prior duodenal ulcer. At the time of diagnosis of the Zollinger-Ellison syndrome, the offending ulcers were in an ectopic location: Jejunal in three (W. M., E. E. and D. G.), postbulbar in four (J. B., L. R., R. L. and C. P.), and stomal in four (A. H., G. P., R. M. and M. S.), and esophageal in two (J. B. and M. S.).

8. The entire spectrum of islet cell growths from simple hyperplasia to multiple primaries with metastases in nine of the patients suggests that these abnormalities are manifestations secondary to another stimulus such as the stomach. In these patients diffuse islet cell hyperplasia without tumor was seen in one (E. E.), an isolated primary islet cell carcinoma without metastases in one (R. L.), islet cell metastases without a demonstrable primary lesion in two (W. M., L. R.), a primary islet cell carcinoma with metastases in four (A. H., G. P., J. B. and D. G.), and multiple primary carcinomata with metastases in one (C. P.). A grossly demonstrable tumor *within* the pancreas was seen in only four patients (A. H., G. P., J. B. and D. G.) and islet cell carcinoma was found *on the surface* of the pancreas in one patient (R. L.).

9. When a tumor of the pancreas was present in this series, none of the islets away from the tumor itself showed atrophy; on the contrary, associated hyperplasia was noted histologically in three patients (J. B., R. L. and C. P.), which suggests that the islet cells are responsive to another stimulus, such as the stomach.

10. The failure to identify a single specific islet cell type in the islet cell tumors suggests another stimulus for growth, such as the stomach. Electron microscopy suggests that the cells usually have characteristics of the Alpha cells.[16] In one tumor in this series a clump of "Beta cells" was found in the midst of a large non-Beta islet cell carcinoma (C. P.); after removal of this tumor in the tail of the pancreas, the patient developed a marked decrease in glucose tolerance, having had normal glucose tolerance prior to removal. Fasting blood sugars were normal before and after operation. An insulin assay of that tumor was positive.[16] Gastrin assay was positive. In another patient (L. R.) the islet cell in the carcinoma metastases in liver, lung and lymph nodes was identified as the "Delta" cell. These tumors contained no gastrin when repeatedly assayed. Nevertheless, the patient had had gastric hypersecretion until total gastrectomy. None of the tumors in these patients were described as composed of carcinoid cells.

11. In this series all patients who had diarrhea and who were treated by total gastrectomy were relieved of this symptom, which suggests that the cause of the diarrhea or steatorrhea is related to gastric acid hypersecretion alone or to a gastric stimulation of islet cell gastrin or other islet cell hormone.

12. Indirect evidence that gastric hypersecretion of acid may stimulate islet cell function is supported by studies in these and other patients in whom glucose tolerance and serum insulin assays have been studied during gastrointestinal administration of acid (0.1N HCl drip supplemented by Histalog injection) or alkaline solutions (soda bicarbonate) in each patient before and after operation. When the environment (pH) of the upper intestine is acid, it appears that there is better glucose tolerance (less hyperglycemia and higher insulin levels) than when it is alkaline. These data suggest that gastric hypersecretion of acid potentiates the islet cell insulin response to glucose. Similar observations have been reported in man[20] and in dogs.[5]

13. There are reports in the literature which indirectly support the hypothesis that a gastric factor is influential in the syndrome. Melnyk *et al.*[21] reported a spon-

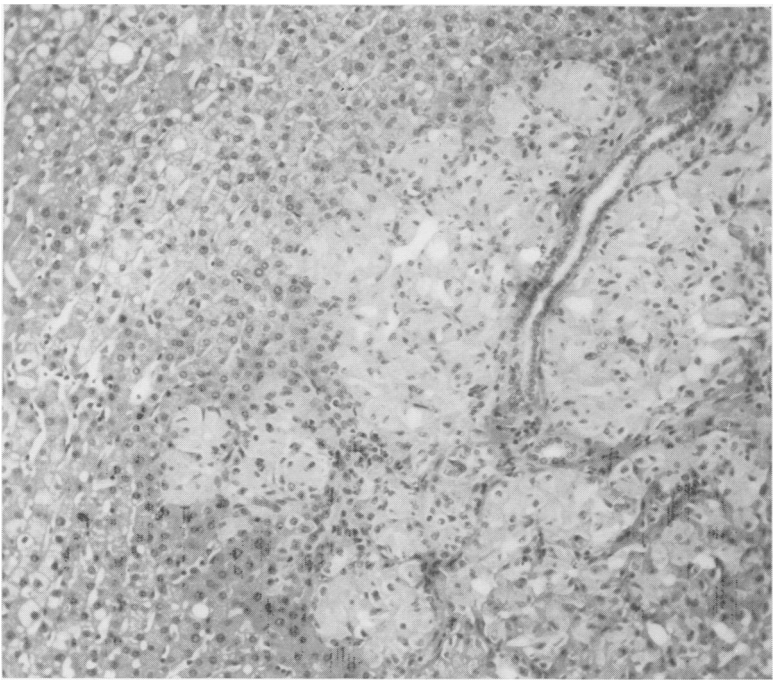

FIG. 5. Photomicrograph of liver metastases from non-Beta islet cell carcinomata of the pancreas in patient C. P. Original magnification × 137.

taneous remission of the Zollinger-Ellison syndrome in a patient in whom only surgical removal of a metastatic lymph node (leaving a large pancreatic tumor in place) and medical treatment by atropine and antacids were followed by symptomatic recovery, healing of ulcers and a 50-pound weight gain in 20 months. Acid secretory values decreased moderately, particularly in concentration values, but radiologic evidence of gastric hyperrugation and duodenal mucosal changes persisted. No observations of any change in the tumor in this patient was made. Shay *et al.*[30] reported temporary symptomatic control in a patient by an anticholinergic drug, yet vagotomy and pyloroplasty failed to prevent the recurrent fatal ulcer complications. Lawrie *et al.*[19] also have reported control of acid secretion in a patient by an anticholinergic agent.

Discussion

Davis[4] described a young man who developed a large liver with proven islet cell metastases 3 years after total gastrectomy for the Zollinger-Ellison syndrome, and 2 years later appeared well without a palpably enlarged liver but with a positive liver scan—a possible "spontaneous regression." In a review of 78 collected cases of total gastrectomy for ulcerogenic tumor of the pancreas, Wilson and Ellison[33] in 1966 stated that there had been only four deaths attributable to tumor and cachexia. They reported that in 248 operative cases the overall influence of gastric secretion is significant: Only 29 per cent were living in whom all gastric mucosa remains; about 50 per cent living in whom subtotal gastrectomy had been done; 73 per cent were living after total gastrectomy; if the initial gastric resection was a total gastrectomy, 87 per cent survived.

The infrequent but important reports of reversal of the syndrome by the excision of a solitary islet cell tumor,[3, 23, 25, 28, 29] applicable to less than 25 per cent of the patients,[8] supports the theory that islet cell changes arise *de novo*, elaborate gastrin, which in turn stimulates the stomach to hypersecrete acid. A significant proportion

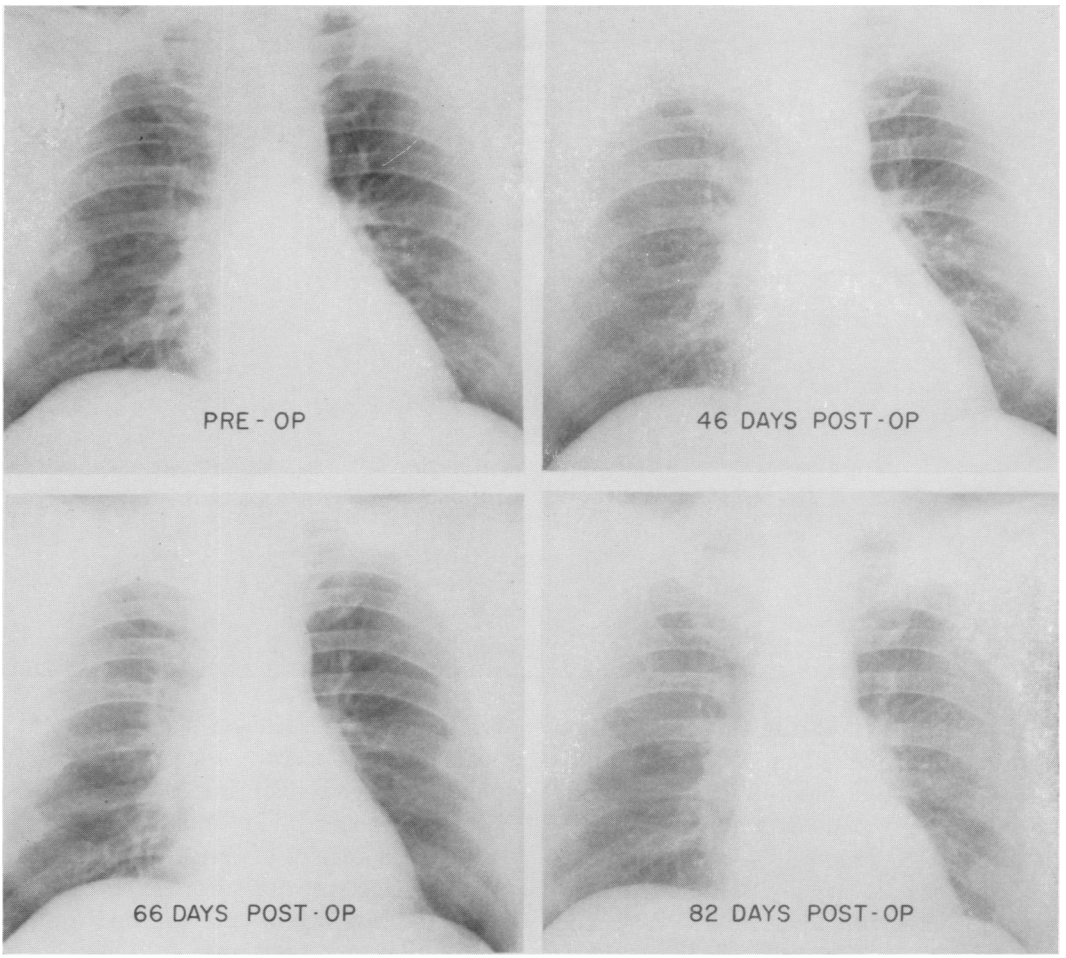

FIG. 6. Chest x-rays of patient C. P. showing regression of islet cell pulmonary metastases after total gastrectomy. A chest x-ray had been negative one year prior to the preoperative film shown here.

(21 per cent) of patients with the Zollinger-Ellison syndrome presents with associated endocrine tumors, usually of the parathyroid glands.[8] When the pituitary also is involved in the multiple endocrine adenomatosis, a hereditary origin has been postulated by Wermer,[32] who has stated that the genetic factor may be a result of abnormal genes and that the various endocrine abnormalities are independent of each other, not under the influence of the pituitary. On the other hand, Rudolph, Dammin and Moore[27] have suggested that the features of the Zollinger-Ellison syndrome may be secondary to pituitary hyperplasia which in turn may be due to an endocrine end-organ failure. Waddell *et al.*[31] have suggested a hypothalamic-pituitary mechanism based on studies of two interesting patients. One of their patients did not survive the effect of the Zollinger-Ellison syndrome after partial blind distal resection of a normal pancreas. An autopsy revealed no abnormalities in the remaining pancreas but an adrenocortical adenoma was present. Studying the histologically normal-appearing pituitary gland, they found abundant stored growth hormone as well as other effects of trophic substances when injected into hypophysectomized rats, as compared to con-

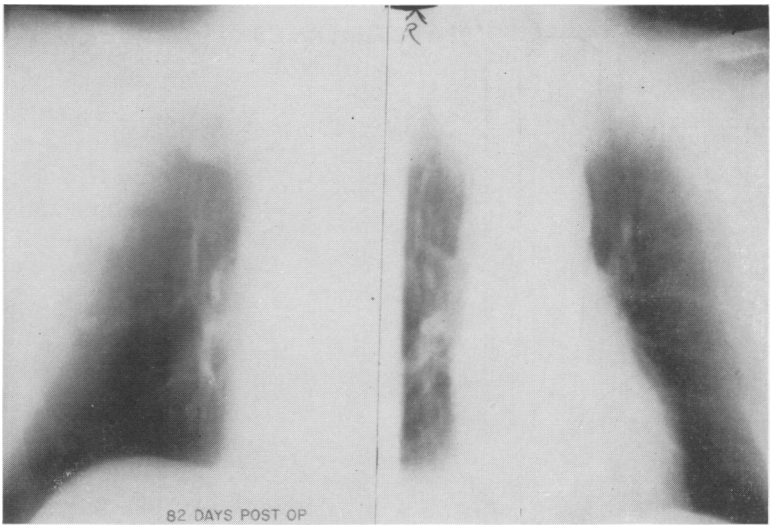

FIG. 7. Planigram, right and left, 82 days after total gastrectomy in patient C. P. Residual lesions are seen (the original films show two on the right and one on the left).

trol studies. They investigated gastric secretion in two patients with the Zollinger-Ellison syndrome and concluded that the secretory phenomena were similar to those found in patients with ordinary duodenal ulcer. They postulated that the gastric hypersecretion was due to unusual autonomic activity due to hypothalamic dysfunction and that through the influence of the hypothalamus upon the pituitary gland the multiple endocrine abnormalities as seen in the Zollinger-Ellison syndrome could be accounted for.

In 1964 Ellison and Wilson[7] stated that 17 of 260 patients with the Zollinger-Ellison syndrome had pituitary lesions, not all of which had evidence of hyperpituitary function. Eiseman and Maynard[9] describe a patient in whom the characteristic features of the Zollinger-Ellison syndrome persisted after excision of three insulin-producing islet cell adenomas, irradiation of a suspected anterior pituitary adenoma, excision of a functioning parathyroid adenoma, and two subtotal gastrectomies and transthoracic vagotomy. Subtotal pancrea-

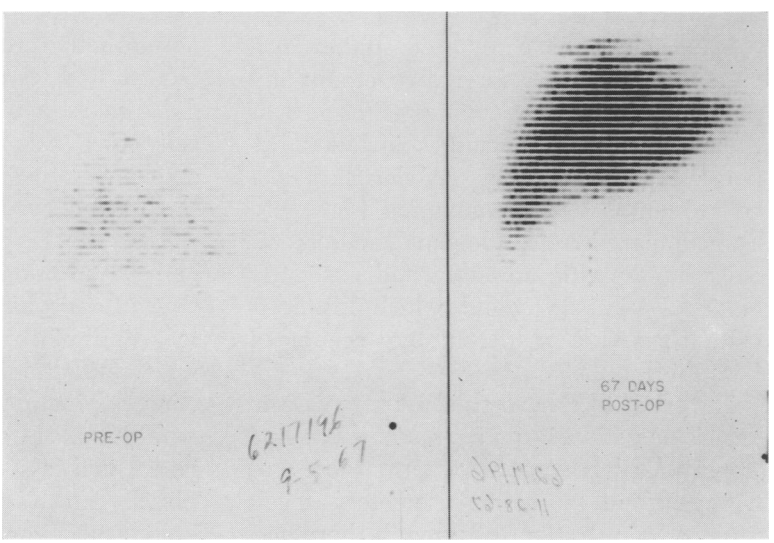

FIG. 8. Hepatic scans (ant.) (Tc-99m) in patient C. P. The preoperative scan is compatible with multiple metastatic lesions. At 67 days after total gastrectomy, the hepatic scan is reported as normal.

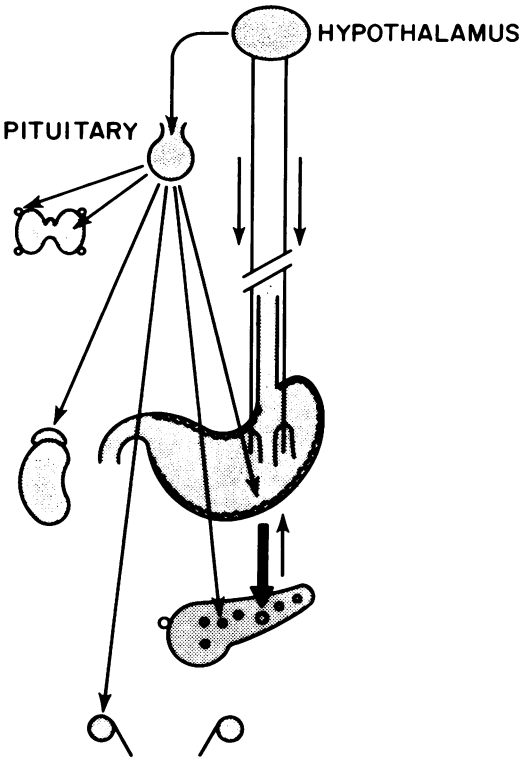

FIG. 9. Diagrammatic representation of a possible pathogenesis of Zollinger-Ellison syndrome and multiple endocrine adenomatosis. A speculative explanation is in the text.

tectomy for a malignant non-Beta islet cell carcinoma plus total gastrectomy of the 5 cm. gastric remnant led to recovery of the patient.

Shay *et al.*[30] have reported studies in a patient who did not survive vagotomy and pyloroplasty for the Zollinger-Ellison syndrome; the autopsy findings included hyperplasia of islet cells (Alpha or Delta cells), lymph nodes containing islet cells, a small parathyroid adenoma, microscopically hyperplastic adrenals, and a slightly enlarged pituitary gland which histologically showed a moderate hyperplasia of basophilic cells.

Robert *et al.*[26] have shown a decrease in gastric secretion in patients who have had trans-auricular hypophysectomy; there was a restoration of normal secretory levels after administration of growth hormone. Goldner and Volk investigated the effects of hypophysectomy and prolonged growth hormone administration upon pancreatic Alpha cells of the rat. Whereas no islet cell changes were noted with hypophysectomy alone, a transitory increase in islet size with a predominantly Alpha cell hypertrophy was noted when growth hormone was given for 3 weeks. When growth hormone was given for 10 weeks, the islet cells became hypoplastic.[13]

Growth hormone assays were carried out in four of the 11 patients in the series reported here, in conjunction with acid and alkaline oral glucose tolerance tests, intravenous glucose tolerance tests and serum insulin assays. Preliminary results indicate that the four patients were all high secretors of insulin with a delayed peak response to glucose. The growth hormone levels were at the upper limits of normal values and did not suppress with glucose. Patient C. P. showed a high growth hormone level which was suppressed by glucose before total gastrectomy, but not suppressed by glucose after total gastrectomy. The typical lag of growth hormone rise was seen after a high peak of insulin and a reactive low blood sugar. Growth hormone levels are higher in patients studied who have hyperparathyroidism.[1] None of the 11 patients had radiologic evidence of an abnormal sella turcica and the visual fields in those tested were normal. Autopsy on J. B. did disclose a pituitary adenoma histologically. G. P. was found to have a co-existent mucus-secreting carcinoma of the stomach surrounded by parietal cell hyperplasia.

Three of 11 patients in this series have had an additional endocrine abnormality. One (L. R.) had Cushing's syndrome due to an adrenocortical adenoma, excision of which failed to modify the Zollinger-Ellison clinical picture. One (C. P.) had hyperparathyroidism due to a parathyroid adenoma and associated parathyroid hyperplasia; after excision, persistence of the Zollinger-Ellison syndrome was evident.

Another patient (W. M.) has evidence of end-organ failure represented by delay of menses and amenorrhea. The increased FSH (follicle-stimulating hormone) in the urine (over 100 mouse units per 24 hours) suggests ovarian failure. Increased 17-ketosteroid and 17-ketogenic excretions were found in two patients (W. M. and C. P.) without a clinical picture of Cushing's syndrome. The blood types of these 11 patients do not appear to have significance: Five had O type, five had A type, and one had B type blood. A preoperative diagnosis of the Zollinger-Ellison syndrome was made in seven of the 11 patients; the serum gastrin assays were not helpful in making the diagnosis. Wilson[34] has reported that 15 of 25 proven cases of the syndrome had negative serum gastrin assays but points out that a positive assay is indicative of the syndrome.

The relationship of the Zollinger-Ellison syndrome to the polyglandular (multiple endocrine adenomatosis) clinical picture is not clear. However, the intermingling of reported observations suggests some sort of relationship. It is probably not too far-fetched to speculate that the entire gamut of variations may be based on a genetic neurohumoral basis (Fig. 9). The common duodenal ulcer diathesis which has strong genetic implications usually is associated with neurogenic autonomic influences via the vagus nerves originating centrally. The hypothalamic dysfunction also acts "internally" to influence the neurohumoral hypophysis.[18] The pituitary thus stimulated could affect the stomach humorally when vagotomy has interrupted the neurogenic influence. The stomach then could stimulate the islet cells. The Zollinger-Ellison syndrome would thus represent an "end-stage" of the duodenal ulcer diathesis. Another possibility is that the pituitary also may stimulate the gastrin-secreting cell of the gastric antrum and the pancreatic islets; this cell may be a neurohumoral ganglion cell, responsive to both vagal and humoral stimulation. The associated endocrine tumors of multiple endocrine adenomatosis may result from pituitary trophic influences or independently by genetic instigation. Similar hypotheses have been previously suggested.[31]

There is a definite close relationship between the stomach and the pancreatic islets, as suggested in 1948 by Poth.[24] Whether the gastric influence upon the islets acts by means of a gastric trophic factor or by the gastric hypersecretion with acidification of the upper small intestine is not clear. In order to elucidate which of these factors is responsible, experiments in single species dogs are being done. Early results seem to indicate that gastric ulcerogenic preparations (Dragstedt[6] antral diverticulum to colon with gastrojejunostomy produce gastric hypersecretion, stomal ulcers and possibly islet cell hyperplasia.[22] Furthermore, studies of the effect of chronic hypothalamic stimulation upon gastric secretion, islet cell changes and the endocrine glands of dogs are being carried out in an attempt to clarify some of the bizarre relationships in the pathogenesis of the Zollinger-Ellison syndrome and multiple endocrine adenomatosis.

Summary and Conclusions

Eleven patients with the Zollinger-Ellison syndrome have been studied with regard to pathogenesis and the mechanism relating the stomach and the pancreatic islets. Evidence is presented to indicate that prompt regression of metastases from non-Beta islet cell carcinomata has occurred following total gastrectomy in a patient having characteristic findings of the Zollinger-Ellison syndrome and hyperparathyroidism. Arrest of tumor growth and complete tumor regression appears to have occurred in at least two other patients who had total gastrectomy. These and other observations suggest that there is a gastric factor affecting islet cells of the pancreas

and that these changes and other clinical features of the Zollinger-Ellison syndrome may represent an end-stage of the duodenal ulcer diathesis. A possible pathogenesis accounting for the many variants of this condition is suggested.

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Discussion

Dr. Robert M. Zollinger (Columbus): I think the one thing that we would all agree upon is that Dr. Friesen has presented a very unusual and stimulating concept. I think it may give moral support to the surgeons who have been afraid to do a total gastrectomy or have been hesitant to do it. Dr. Ellison and I in talking about this many times have wondered how so many lesser and inadequate operations have been carried out.

I have two pictures to show of one of the original patients presented before this Association in 1955, who had metastatic tumor in a lymph node on the surface of the pancreas [first slide]. We never found a primary pancreatic tumor. She has now "metastasized" otherwise, as you can tell, with two children at 7 and 8 years after the total gastrectomy, and is now in her fourteenth postoperative year.

[Next slide] She was re-explored after 10 years during a cholecystectomy because of gallstones. We searched for evidence of the tumor, hoping not to find any but afraid we might. A portion of the tail of the pancreas was resected for study, [next slide]. This slide shows a microadenoma which was found in the pancreas, but no gross evidence of tumor in the pancreas or elsewhere was found. I can not help but wonder—well, several things occur to me as a matter of fact.

One, why do we sometimes find only microscopic evidence of metastasis in the adjacent lymph nodes without gross evidence of tumor in the pancreas? How do you explain this? I wonder why the pathologists can't give us an answer? Two, I wonder why these people do so well after total gastrectomy and maintain their nutrition and do better than they should. This is a common observation, and I am not quite clear why this occurs after total gastrectomy to control the ulcer diathesis. I like this concept of Dr. Friesen. I don't know that I believe a word of it, but I'd like to thank him.

Dr. Edwin H. Ellison (Milwaukee): First of all, I want to thank all of you for helping us maintain an ulcerogenic tumor registry which we have maintained since we presented this concept 13 years ago. We now have over 600 proven cases of the Zollinger-Ellison Syndrome in the registry; 120 of these are living and well after total gastrectomy. Those that die after total gastrectomy, for the most part, die early as a result of technical failure of the surgeon because he is operating upon the patient for the fourth or fifth time.

In children that we have in the registry, none are living who have not had total gastrectomy, so it seems as if this is a more serious disease in children but it responds better to total gastrectomy. These children continue to grow and some of them have had children. So I think that the data is gradually collecting to indicate that Stan Friesen may have a point, that removal of that end organ, although he is saying it in a different fashion, does have an influence on the growth of tumors. Certainly the ones I have seen personally and have done total gastrectomies for them are still living and the tumors have not grown.

Dr. Stanley R. Friesen (Closing): I am glad Dr. Zollinger likes the concept, whether he believes it or not. I appreciate all the assistance I have had from him and Dr. Ellison and their associates and the many people who have done the assays for me.

Dr. Zollinger has raised some very interesting questions regarding the tumor itself. Our pathologists have described very frequently the picture of hyalinization in the islets. I do not know what this means, but the word crops up often enough to make it interesting if not significant. Whether the gastric influence on the islets is just marked hypersecretion of acids or a trophic substance liberated either from the stomach or the duodenum is not known.

We are carrying out two sets of experiments in the laboratory on dogs to try to elucidate which of these mechanisms is present. Dogs which have a gastrin ulcerogenic preparation such as described by Oberhelman and Dragstedt (the antral diverticulum on the colon), do develop hypersecretion of acids and stomal ulcers. In these animals we are studying the pancreas for the development of hyperplasia of the islets. Another group of dogs are having hypothalamic stimulation chronically and in these dogs we are going to watch the endocrine organs and specifically the stomach and the islets of the pancreas.