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Mechanism of the Gastric Hypersecretion in the Zollinger-Ellison Syndrome:

Successful Extraction of Gastrin-Like Activity from Metastases and Primary Pancreatico-Duodenal Islet Cell Carcinoma *

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IT IS BECOMING apparent that a humoral mechanism underlies the gastric hypersecretion shown by patients with the Zollinger-Ellison syndrome, which is responsible for the intractable ulceration usually present. Furthermore, it appears that the source of this humoral agent is in the islet cells of primary tumors and their metastases, when present, and that the end organ is the parietal cell mass of the mucosa of the stomach.

The existence of a humoral mechanism is suggested by the many reports in the literature in which marked gastric hypersecretion of acid (over 100 mEq. HCl in 12 hours fasting aspiration) has been associated with islet cell noninsulin-secreting tumors of the pancreas or the duodenum.[14,23] At least seven cases have been reported in which control of the ulcer diathesis (reduction of gastric hypersecretion to normal levels and healing of the ulceration) followed complete surgical excision of nonbeta islet cell tumors of the pancreas or duodenum, or hepatic metastases.[11,14,17,25] Additional cases have been reported in which intractable diarrhea and steatorrhea due to marked gastric hypersecretion of acid without ulceration was controlled by excision of nonbeta islet cell tumor or by total gastrectomy.[12,17,21]

Peptic ulceration has been shown to be present in about 13 per cent of cases of hyperparathyroidism with inconsistent findings of gastric hypersecretion.[24] Excision of a parathyroid adenoma in such cases usually leads to healing of the ulcer.[15,24] However, there have been at least two cases in which the ulcer diathesis persisted after removal of the parathyroid adenoma until total gastrectomy was performed; in these cases there were associated nonbeta islet cell adenomas.[3,24] Peptic ulceration also has been shown to be associated with

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polyglandular endocrine adenomas (pituitary, parathyroid, pancreatic islet of both beta and nonbeta cells). Zollinger and Craig[24] pointed out that of 17 cases in the literature in which peptic ulceration was associated with the polyglandular syndrome, 13 were studied subsequently by operation or autopsy and all had non-insulin producing islet cell tumors of the pancreas.

Physiological and chemical studies based on extraction of primary nonbeta islet cell tumors of the pancreas strongly support the humoral theory of the mechanism of gastric hypersecretion of acid. Gregory, Tracy, French and Sircus[8] reported that an islet cell adenoma from a patient with Zollinger-Ellison syndrome contained large amounts of a substance which in its chemical and physiologic properties resembled the antral hormone, gastrin. This substance, extracted by a method which extracts gastrin from hog antral mucosa,[7] stimulated the secretion of gastric acid but not pepsin in dogs and was found to be 33 to 45 times as potent, gram-for-gram, as hog antral mucosa; the activity of the preparations was not due to the presence of insulin or histamine. The removal of the solitary ulcerogenic adenoma of the pancreas caused a prompt relief of ulcer symptoms in the patient without other operations for ulcer having been done.[17] Grossman, Tracy and Gregory have isolated a gastrin-like substance from the primary and secondary tumors of a patient with the Zollinger-Ellison syndrome.[9] Code, Hallenbeck and Summerskill have confirmed these studies by the extraction of histamine-free gastrin from hog antral mucosa and from the tumors of two patients with the Zollinger-Ellison syndrome.[1] Other attempts at extraction of such tumors have not always been successful, but Osborne, Brown and Le Compte[16] prepared a saline extract of a nonbeta islet cell pancreatic carcinoma which lowered the pH of Heidenhain pouch secretion of a dog from neutral to 1.6 within the first hour; similar extracts of normal human liver and pancreas were without effect. Chemical analyses of the extract showed only traces of histamine. Hirschowitz[10] recently has tested a simple saline extract made from a tumor obtained by Schenker of the National Institutes of Health and has found high gastrin-like activity in it.

Wermer has called attention to a polypoid appearance in the duodenum as visualized by x-ray studies as suggestive evidence of islet cell tumors in or adjacent to the duodenal wall.[27] "Isletization" or hyperplasia of the islets of the pancreas have been reported in conjunction with islet cell tumors of the duodenum.[14]

It is not known which of the islet cells is responsible for the secretion of the humoral gastric stimulant. Glucagon, the hyperglycemic, glycogenolytic substance secreted by the alpha cells, has been shown to cause a reduction of gastric secretion in dogs and man when injected intravenously, and is considered not to be ulcerogenic.[2,17,19]

The changes in the end-organ, the stomach, have been reported to be similar in appearance to the giant rugae of Menetrier's disease,[13] mucosal hypertrophy of the stomach. The stomach in the Zollinger-Ellison syndrome, however, secretes large volumes of highly acid juice and the mucosal changes consist of thickening due to a marked increase in the numbers of parietal cells, a hyperplasia.[24]

Other evidence supporting a humoral mechanism consists of the reports of the failure of vagotomy and antrectomy to control the acid hypersecretion.[26] Zollinger has pointed out that the pituitary-adrenal axis overactivity theory seems unlikely because the level of steroid excretion invariably has been low when studied.[24] Rudolph, Dammin and Moore[20] postulated that pituitary hyperplasia or adenomatous change due to failure of an endocrine end-organ may cause an increased production of one or more of the trophic hormones. The trophic hormones cause hyperplasia or adenomas of the other target endocrine

organs. The acid-peptic axis then is stimulated directly through antral activity and parietal cell hyperplasia, or indirectly as a by-product of secretion of the adrenals, gonads or parathyroids.

That tumors are capable of liberating a substance having a humoral activity which is not expected from their cell structure is exemplified by the reports of clinical and extraction studies of hypoglycemia-producing mesotheliomas from which extractions demonstrate an insulin activity.[4]

Because of the strong evidence for a humoral mechanism underlying the gastric hypersecretion in patients with Zollinger-Ellison syndrome, it would be highly desirable to show by extraction studies that metastatic lesions of nonbeta islet cell carcinoma also contain histamine-free gastrin activity and that nonislet cell acinar carcinoma of the pancreas with metastases do not show such activity. It is the purpose of this paper to report such findings.

Case Report

J. B., No. 60-16504, a 41-year-old Negro man, was admitted to the University of Kansas Medical Center on November 26, 1960, and dismissed on December 14, 1960.

The patient, a clothes-presser, was admitted to the hospital with the chief complaint of pain in the upper abdomen and weight loss of two and one-half months' duration. The onset of these complaints was rather sudden and consisted of frequent sharp pains in the epigastrium radiating to the back. The pain was relieved by the ingestion of milk and anti-acids. The pain would occur at all hours of the day or night and could be relieved by assuming the knee-chest position. The patient stated that he vomited blood on one occasion two weeks prior to admission but otherwise he denied nausea, vomiting, tarry stools, diarrhea or jaundice. There was a 42-pound weight loss within the last two and one-half months. He also complained of low back pain radiating down the left leg.

Two weeks prior to this hospitalization the patient was hospitalized elsewhere because of the low back pain. The patient stated that he was told that he had "a ruptured vertebra" but that operation for this was not carried out because his blood count was too low (hemoglobin of 4.5 Gm.%). At that hospital an upper gastrointestinal x-ray series was done which demonstrated a large ulcer crater between the third and fourth portions of the duodenum. He was treated with anti-acids and anticholinergic agents and was given four units of whole blood and transferred to the University of Kansas Medical Center for further management of the duodenal lesion.

The past history revealed that a diagnosis of "peptic ulcer" was made in 1956 at St. Paul, Minnesota, for which he was treated with anti-acids with satisfactory relief. In the interval of time between 1956 and the present admission he had complained only of occasional epigastric pain, usually after the ingestion of alcohol, with prompt relief with anti-acids. He had not drunk alcohol for the past year.

There was no family history of ulcers or cancers. He smoked one to two packages of cigarettes a day. There was no history of allergies, other medications, or surgical procedures. There were no cardio-respiratory symptoms. There were no symptoms suggestive of hypoglycemia.

Physical examination at the time of admission revealed a well developed but emaciated male, appearing acutely and chronically ill, with a clear sensorium. The skin was dry. The mucous membranes were pale and without evidence of jaundice. The blood pressure was 110/85, the pulse 110/min. with regular rhythm, and the respirations were 16/min. The head, neck and chest were normal with the exception of palpable lymphadenopathy (three 2–3 cm. hard nontender nodes) in the left supraclavicular area, and a Grade I systolic murmur along the left sternal border without a palpable thrill. The abdomen was protuberant and distended, tympanitic to percussion, with normal bowel sounds on auscultation. No masses were palpable. There was a suggestion of shifting dullness in the flank. There was no tenderness. Rectal examination revealed a normal sized prostate without other masses. Examination of the back suggested spasm of the left paraspinous muscles. On standing, the patient leaned to the left and put little pressure on the left leg. There was weakness of the left iliopsoas and quadriceps muscle groups and the left deep tendon reflexes were absent. The position ties were normal.

Laboratory values on admission to the hospital sense was intact. All other findings in the extremi- included Hgb. 7.2 Gm.%, hematocrit 29 cc./100, reticulocytes 2.2, platelets 206,000, WBC 12,600, 82% polymorphonuclear; urinalysis normal, blood urea nitrogen 6 mg.%, cretinine 1.3 mg.%, HCO_3 32.8 mEq./L., sodium 134 mEq./L., potassium 3.2 mEq./L., chloride 92 mEq./L., calcium 4.5 mEq./L.; prothrombin time 65% of normal; sickle cell preparation—positive with sodium bisulfide;

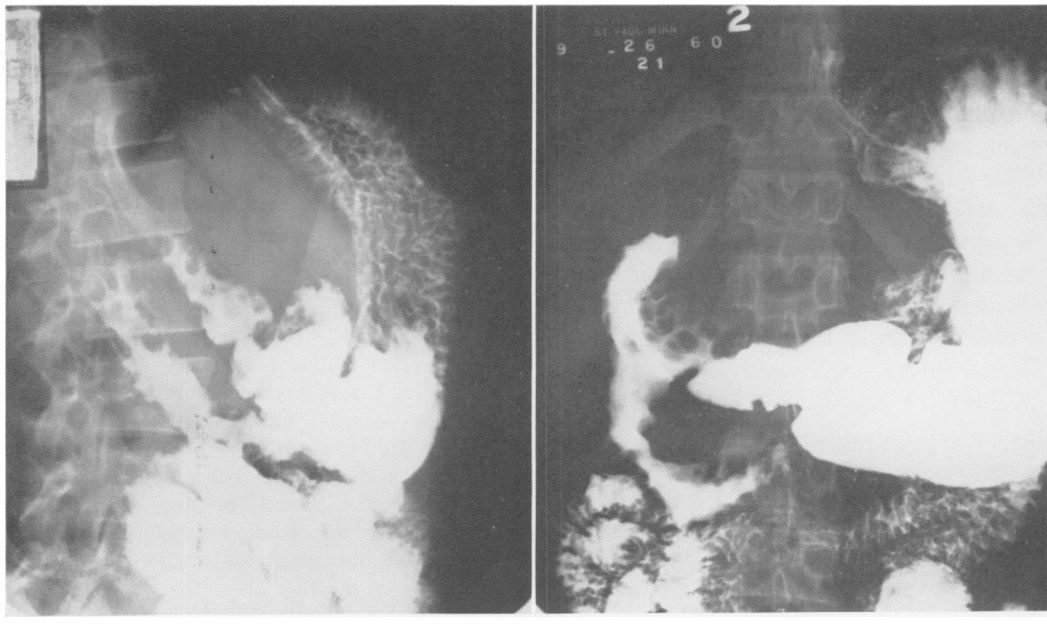

FIG. 1. Left: X-ray taken in November 1956, illustrating the hypertrophic rugae of the stomach and the polypoid changes in the duodenum of patient J. B. Right: X-ray taken in September 1960, illustrating the findings seen in 1956 with the addition of duodenal loop deformity with suggestive ulcerations of the 3rd portion of the duodenum and lower esophagus.

serum amylase 270 units, serum lipase 0.4 units, serum bilirubin 0.5 mg. total. Gastric analysis–free acid 112 mEq./L., total 24 hour volume 5,900 cc. Blood group O, Rh positive; stool for blood 2+ guaiac; urinary 5-hydroxy-indole-acetic acid–negative. Serum proteins, total 7.75 Gm.%, albumin 3.48 Gm.%, globulin 4.27 Gm.%. Fasting blood sugars obtained later were reported as 75, 80 and 86 mg.% on three separate occasions.

A review of the x-rays taken at other hospitals prior to admission included the findings of hypertrophic rugae of the stomach, polypoid changes in the first portion of the duodenum, a normal duodenal loop, a functioning gallbladder, normal chest in November 1956, and January 1957. In September 1960, x-rays revealed, in addition to the above, a widened duodenal loop with an ulcer in the third portion of the duodenum, an ulcer of the esophagus, and a normal myelogram (Fig. 1). Additional x-rays taken on admission showed an apparent ileus with suggestive intraperitoneal fluid, a normal intravenous pyelogram, and a normal spine. A lateral of the skull, taken since dismissal from the hospital, demonstrated a normal sella turcica.

The left supraclavicular nodes were removed for biopsy and microscopic examination revealed metastatic malignancy resembling islet cell carcinoma. The patient was placed on nasogastric suction and volumes between 4,000 and 5,900 cc. were aspirated daily which contained 150 mEq. sodium, 47 mEq. potassium and 760 mEq. chloride in 5,350 cc. The patient required the transfusion of nine units of whole blood within the first five days after admission, at which time the hemoglobin value reached 14.4 Gm.% and the hematocrit 46 cc./100. A diagnosis of Zollinger-Ellison syndrome secondary to islet cell carcinoma, metastatic, was made. Because of coffee-ground material present in the gastric aspirate, the melena and the continuously severe epigastric pain, the patient was considered a candidate for surgical intervention for palliation.

On the seventh hospital day an operation was performed,* at which time exploration revealed a large mass in the head of the pancreas with lymph node and hepatic metastases. A large ulcer, 2.0 cm. in diameter, was present in the third portion of the duodenum. The stomach wall was greatly hypertrophied and the duodenal wall was thickened. Because of the metastases present it was thought that neither pancreaticoduodenectomy nor total gastrectomy was justified. It was hoped that sufficient temporary control of the ulcer diathesis could be obtained by vagotomy and subtotal (75%) gastrectomy–Hofmeister, Billroth II, retrocolic, short proximal loop. In addition, a duodenotomy was done to facilitate biopsy of the pancreas through the duodenal ulcer, with

* Operation by Dr. William Hall, Senior Resident in General Surgery.

suture of the ulcer. Biopsies of metastatic lymph nodes and liver lesions also were obtained for microscopic confirmation, and tissues of the pancreas, lymph gland and hepatic nodules were placed in picric acid solution and sent to Liverpool for extraction and assay of gastrin-like activity. The microscopic examination demonstrated islet cell carcinoma of the pancreas involving the duodenum, with lymph node and hepatic metastases (Fig. 2). The microscopic appearance of the stomach mucosa showed a preponderance of parietal cells (Fig. 3).

Following operation the patient recovered without complications and had no further bleeding. He received 25 mg. nitrogen mustard intravenously over a period of five days. The hemoglobin value during this time fell to 10 Gm.%, but the platelets remained above 250,000 per cu. mm. The back and leg pain were absent postoperatively and the patient was able to walk without difficulty. The patient was dismissed from the hospital on the 12th postoperative day.

On December 28, two weeks after dismissal, the patient returned to the hospital complaining of epigastric and right upper abdominal pain which disappeared within 24 hours of hospitalization. Upper gastro-intestinal x-ray series revealed a normally functioning gastrojejunostomy and hypertrophic rugae of the gastric remnant. He was dismissed to his home in Minnesota.

Case for Control Studies

R. C., No. 60-15694, a 68-year-old Negro woman, was admitted to the University of Kansas Medical Center on March 2, 1961, and dismissed on April 5, 1961. The patient complained of upper abdominal pain for four and one-half months and jaundice of two weeks' duration. Diagnostic studies were noncontributory. The serum bilirubin was reported as direct, 4.5 mg.%, total 7.5 mg.%. There was no evidence of gastric hypersecretion, peptic ulceration, or hypoglycemia. A clinical diagnosis of carcinoma of the pancreas was made and exploratory laparotomy was done on March 7, 1961.† A malignant tumor of the pancreas with hepatic metastases was found. Biopsies were taken and a palliative cholecystojejunostomy en Roux-Y was performed. The microscopic examination of the biopsy material showed poorly differentiated acinar adenocarcinoma of the pancreas and liver. Tissue from the pancreatic tumor and the hepatic metastases were placed in picric acid solution and sent to Liverpool for analysis of gastrin-like activity.

Tissue Extraction Studies

The moist weights of the specimens provided for extraction were as follows:

† Operation by Dr. Don Miller, Department of Surgery.

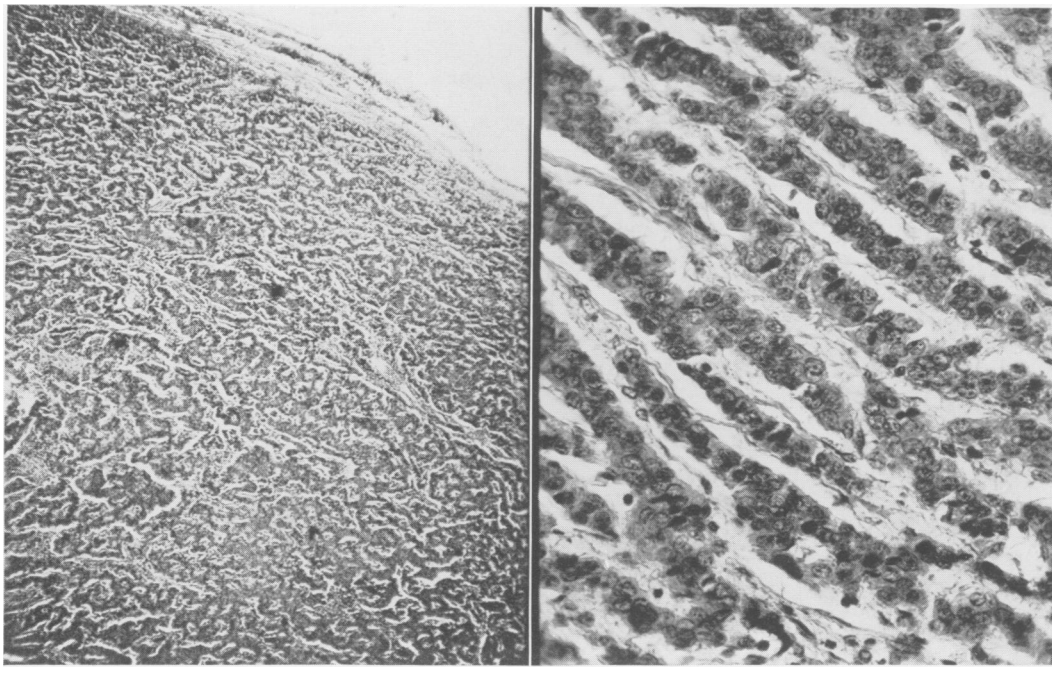

FIG. 2. Left: Photomicrograph illustrating low power view (from × 60) of metastatic islet cell carcinoma. Right: High power view (from × 425) of the same. Note the cord-like arrangement along capillaries and the pleomorphism of the cells.

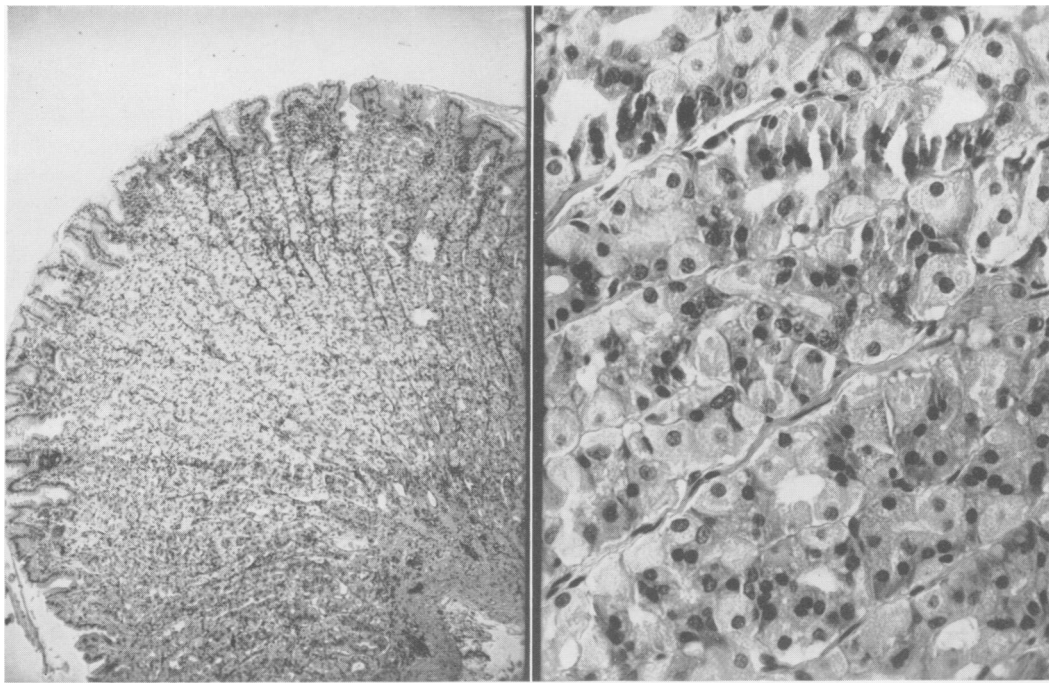

FIG. 3. Left: Photomicrograph illustrating a low power (from × 60) view of the thickened gastric mucosa. Right: A high power (from × 425) view illustrating the preponderance of parietal cells in the gastric mucosa.

Pancreatic primary	0.24 Gm.
Hepatic secondary	0.15 Gm.
Lymph gland secondary	1.63 Gm.

Each tissue was removed from the picric acid and cut into the smallest possible fragments with a razor blade. It was then extracted by a procedure which is described in full by Grossman, Tracy and Gregory.[9] This involves exhaustive extraction with a solution of four per cent trichloro-acetic acid in 75 per cent aqueous acetone, recovery of the aqueous residue left after repeated ether extraction, and repeated precipitation with trichloroacetic acid. The final produce in each case was a clear solution in approximately isotonic NaCl solution, volume 4.0 ml. and pH 8.5. This method of extraction is a modification of the first stage of the procedure evolved by Gregory and Tracy[7] for the extraction from hog antral mucosa of the hormone gastrin. Because of the very small weights of the tissue specimens it was deemed advisable to administer almost the entire extract of each as a single subcutaneous injection to a conscious pouch dog; a small aliquot (one-twentieth) of each was set aside for histamine assay.

The dog used for the tests was provided with a completely denervated fundic pouch;[6] it was the same animal as that designated by Gregory, Tracy, French and Sircus[8] as "dog No. 2" and by Grossman, Tracy and Gregory[9] as "dog No. 1." Its sensitivity to injections of gastrin, histamine and preparations from Zollinger-Ellison tumors was thus well established. It had also been established that this animal gave no secretory response to a subcutaneous injection of 20 units of ordinary insulin, although the blood sugar fell to a low level.

On the occasion of the injections the dog had been fasted for 20 hours; there was no basal acid secretion from the pouch. The responses to injection in turn of the three extracts (from patient J. B.) are shown in Figure 4. The lymph-gland extract was injected first. There ensued a prompt acid secretory response, which lasted approximately 90 minutes. Injection of the primary extract was followed by a similar response of appreciably smaller magnitude, lasting approximately 60 minutes. Finally the hepatic secondary was injected; this produced only a slight though quite definite effect. None of the injections was followed by any discernible side-effects whatever in the dog.

Histamine assays using the isolated guinea-pig ileum preparation were performed on the extracts of pancreatic primary and lymph gland secondary; the extracts contained less than 0.01 μg. histamine base per ml. The aliquot of the hepatic secondary unfortunately was lost by accident. The possibility that these responses were

due to the presence of insulin in the extracts is excluded by the fact, as mentioned above, that the completely denervated fundic pouch used for the tests did not secrete when the dog was given a subcutaneous injection of insulin.

As a control to these studies, primary and secondary tumor extracts were similarly made and similarly tested, from a patient (R. C.) with carcinoma of the pancreas who showed no evidence of the Zollinger-Ellison syndrome. These extracts were completely inactive.

The results leave little doubt that the responses obtained with all three tissue extracts from the case described (J. B.) were due to the presence of gastrin-like activity; the protracted time-course of the secretory response, even though the total magnitude was small, is characteristic of gastrin and the gastrin-like activity of Zollinger-Ellison tumor extracts after subcutaneous injection.

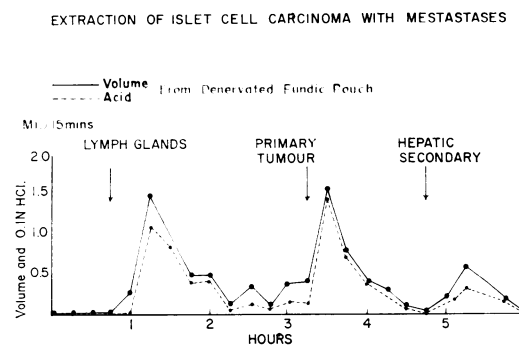

FIG. 4. Response of the denervated fundic pouch to the subcutaneous injection of the extracts of the islet cell carcinoma and its metastases from the patient with the Zollinger-Ellison syndrome.

Discussion

The clinical aspects of the case report (J. B.) are interesting in that a clinical diagnosis of peptic ulcer was made in another hospital four years prior to the present study. At that time, November 1956, radiologic studies revealed the giant rugae of the stomach, the knobby polypoid appearance of the duodenum without widening of the duodenal loop. In September 1960, there was an appearance of a widened duodenal loop, an ulcer of the third portion of the duodenum, and a suggestion of an ulcer of the terminal esophagus. From a clinical standpoint it is difficult to determine whether the primary lesion was entirely pancreatic with invasion of the duodenal wall or whether there has been malignant transformation of duodenal islet cell rests with invasion of the pancreas. The large size of the mass in the head of the pancreas, however, suggests that the primary origin was within the pancreas itself. The knobby appearance of the duodenum on x-rays was considered at first to be due to hyperplasia of islet cell rests in the duodenum, but histologic study suggests a hypertrophy of Brunner's gland as the cause of the nodularity.

The giant gastric rugae frequently seen in patients with Zollinger-Ellison syndrome sometimes has been referred to as Menetrier's disease, or as gastric polyposis. Neither of these terms accurately describes the histologic, histochemical or functional changes in the hyper-secreting gastric end-organ associated with nonbeta islet cell tumors. According to Goodale and Sniffer,[5] the mucosal hypertrophy of the stomach in Menetrier's disease consists of elongation of gastric glands with retention of the normal pattern and cellular detail; these patients secrete a normal or below normal amount of gastric acid.

Conclusion

A substance having physiological and chemical properties similar to those of gastrin has been extracted from a pancreatico-duodenal islet cell carcinoma and its lymph node and hepatic metastases in a patient having the Zollinger-Ellison syndrome. No histamine activity was demonstrable in this extract. This is the first demonstration of gastrin activity from lymph node metastases of islet cell tumor. Similar extractions from an acinar adenocarcinoma with metastases, in a patient without the Zollinger-Ellison syndrome, failed to show gastrin activity.

The patient reported here demonstrated several of the clinical features of the Zollinger-Ellison syndrome, including metastatic islet cell carcinoma of the pancreas, duodenal nodularity, ulceration of the third portion of the duodenum and of the termi-

nal esophagus, and the associated changes in the end-organ of giant gastric rugae, parietal cell hyperplasia and marked hypersecretion of gastric acid.

The extraction studies lend strong support to the humeral theory of the mechanism of gastric hypersecretion in the Zollinger-Ellison syndrome.

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