Primary Peptic Ulcerations of the Jejunum Associated with Islet Cell Tumors of the Pancreas*

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FORTUNATE INDEED IS the surgical service that does not have one or more problem cases of recurrent marginal ulceration despite the adequacy of the surgical attack. These unfortunate few not only harass the individual surgeon but tend to humble those who advocate a so-called ideal surgical procedure for the control of the acid-peptic factor. On rare occasions repeated gastric resections, combined with vagotomy below, as well as above, the diaphragm, fail as the patient becomes more and more miserable, and his hospital chart more and more voluminous. It is understandable that everything must be tried before subjecting such a patient with a benign lesion to the highly unsatisfactory status of post-total gastrectomy. In the past two years we have observed two such problem cases of benign ulceration of the upper jejunum associated with extremely high gastric acid production over a 12-hour period. Primary ulcerations of the upper jejunum are perplexing problems, just as are the ulcers which occur in the second or third parts of the duodenum, or the marginal ulcer which occurs despite vagus section and an almost total gastrectomy. In the two cases to be reported gastric hypersecretion could not be controlled by the usual surgical measures, and marginal ulceration recurred until total gastrectomy became mandatory. Of particular interest is the fact that a non-Beta cell adenoma, with no clinical or laboratory evidence of insulin production, was found at the time of autopsy in one patient, and at the time of total gastrectomy in the surviving patient. The finding of islet cell adenomas associated with almost unbelievable levels of 12-hour nocternal gastric secretion despite complete vagus section and radical gastric resection recalls to mind the suggestion of Poth[15] and the studies of Dragstedt[4] and Elman[3] regarding the possible role the pancreas may play in the etiology of peptic ulcer. The detailed case reports are presented, along with some preliminary observations designed to test the possibility of a direct relationship of these pancreatic lesions to a pancreatic phase of gastric hypersecretion.

Case 1. C. P., a 36-year-old married white female, was first admitted to the medical service of University Hospital, Columbus, Ohio, on July 22, 1952, with the chief complaints of abdominal pain and diarrhea of 8 years' duration. During this long period she had complained of general abdominal distress and the passage of from 3 to 10 liquid stools daily. Her first hospitalization led to a diagnosis of spastic colitis. Gastro-intestinal roentgenograms and stool cultures were repeatedly negative. Despite therapy with sulphonamides and antibiotics, the symptoms persisted.

In 1949 her symptoms changed and she developed a gnawing, right-sided epigastric pain and fullness which led to a second hospitalization. Milk and antacids brought only temporary relief. After barium studies failed to demonstrate either a gastric or a duodenal ulcer, a diagnosis of chronic gastritis was made. The patient's complaints were partially controlled by an intensive Sippy regimen, combined with antacids and a variety of vagal blocking agents designed to control the suspected gastric hyperacidity.

One year later in 1950, following a period of increased abdominal distress, the first of several episodes of melena was noted. Vomiting of coffee-

* Presented before the American Surgical Association, Philadelphia, Pa., April 29, 1955.

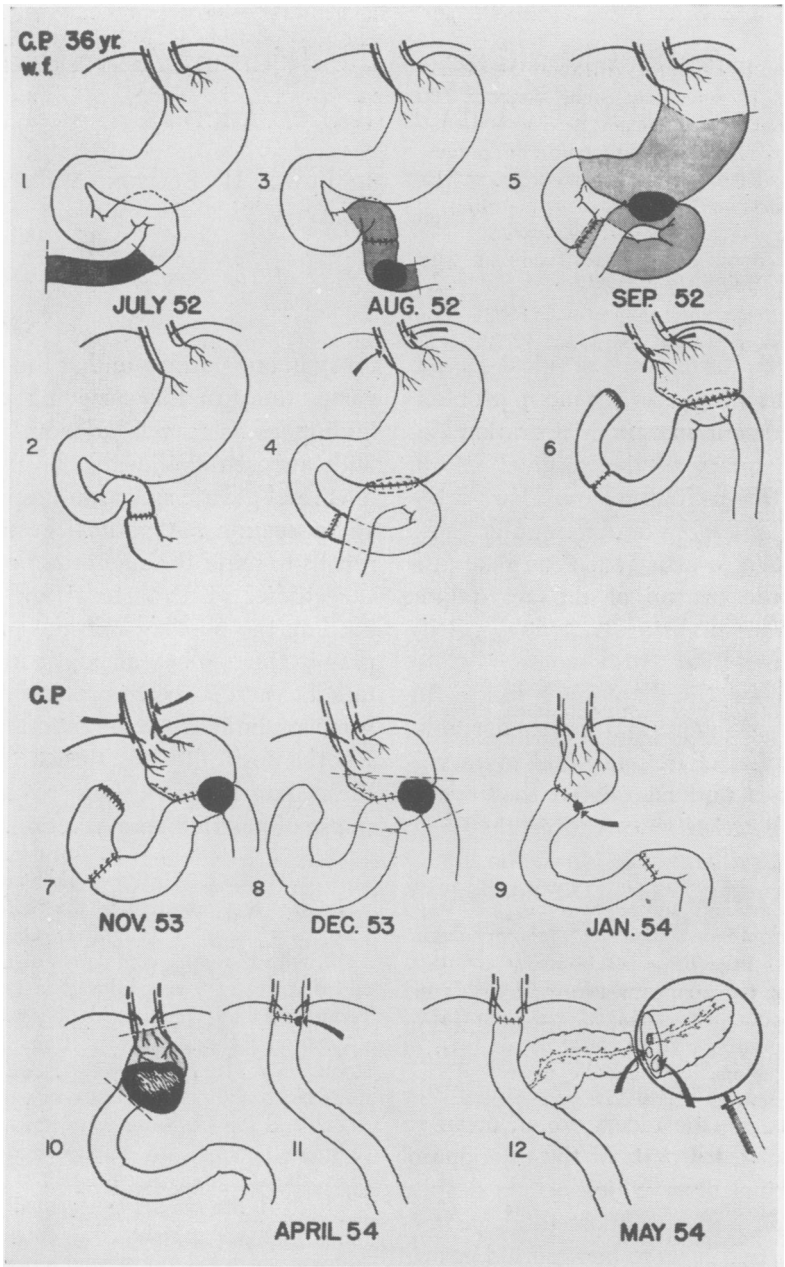

FIG. 1. Schematic representation of clinical course of Case 1 (C. P.), including sites of recurrent ulcerations and operative procedures through total gastrectomy. The pertinent autopsy findings are indicated in Diagram 12.

grounds material led to more intense ulcer therapy, and the bleeding subsided. The patient's course remained unchanged for the next two years. However, decreased appetite and subsequent vomiting led to a 14-pound weight loss in less than one month, prior to admission to University Hospital.

A system review and past medical history offered no additional information. The family history was of interest in that the patient's father had died following operation for gastric ulcer. The mother was living and well following operation for a duodenal ulcer several years previously. A younger sister had

died at the age of 22 years, apparenty from hyperinsulinism.

On admission to University Hospital the patient measured 5 feet 7½ inches in height, weighed 100 pounds, and appeared chronically ill. The abdomen was moderately distended, tympanitic to percussion, and no masses could be palpated. There was marked tenderness and some muscle guarding in the epigastrium along the left costal margin.

The red blood cell count was 4.1 million, with 11 Gm. of hemoglobin. RIHSA blood volume measurements indicated a total deficit of 1718 ml. The white blood count varied between 12,700 and 19,200.

A fasting blood sugar of 125.5 mg./100 ml. led to an oral glucose tolerance test, which resulted in a diabetic type of blood sugar curve with a normal fasting value. The blood sugar levels were: fasting, 92 mg. per cent; at one-half hour, 135 mg. per cent; at one hour, 233 mg. per cent; at two hours, 201 mg. per cent; at three hours, 193.5 mg. per cent; and at four hours, 103 mg. per cent. A trace of sugar was found in the urine during the third hour.

A 12-hour nocturnal gastric aspiration yielded a total volume of 2000 ml., with 82 clinical units of free HCl and 95 clinical units of total HCl. The total free acid for the 12-hour period was calculated to be 164 mEq. (Fig. 2). The guaiac tests for occult blood were positive in all gastric specimens.

The mucosal pattern of the stomach and duodenum was coarsened and edematous, and suggested hypertrophic gastritis by roentgenologic examination. An area suspected of being an ulcer was noted along the pancreatic side of the first part of the duodenum. The stomach was two-thirds empty at 30 minutes, with the head of the barium column in the ileum. The mucosal pattern of the small bowel showed segmentation and irregular barium-filled loops with widening and narrowing. These findings, together with a history of multiple stools, suggested a sprue-like syndrome. In retrospect, a large, air-filled ulcer crater of the proximal jejunum could be outlined just above the lesser curvature, and behind the barium-filled stomach.

Epigastric and left paraumbilical pain persisted despite a modified Sippy regimen combined with sedation and antacid therapy, and required an increasing amount of narcotics for relief. Laparotomy was considered indicated, with the preoperative diagnoses including chronic duodenal ulcer and possibly chronic recurrent pancreatitis.

On August 6, 1952, following restoration of the blood volume and serum protein deficits with whole blood and human serum albumin, the abdomen was explored. The stomach was moderately thickened and dilated, as were the first and second parts of the duodenum. A duodenal ulcer, however, was not demonstrated. The dilatation persisted beyond the ligament of Treitz for a distance of some 18 cm., where an ulcerating lesion of the bowel with partial obstruction was found. The proximal jejunum was thickened, congested and edematous, and was folded upon itself at the site of obstruction. Induration, which later proved to be hemorrhage into the mesentery at this site, gave the impression that a malignant process, possibly a lymphoma, was the etiologic factor. The mesenteric nodes in the immediate vicinity were markedly enlarged, and were diagnosed as lymphadenitis on frozen section. The ligament of Treitz was divided, permitting mobilization of the lower part of the duodenum and allowing wide resection of the obstructing lesion, together with as much mesentery as feasible. Continuity was re-established with an end-to-end anastomosis (Fig. 1, Diagrams 1 and 2).

A sharply punched-out ulceration, measuring 2 cm. x 1 cm. in its greatest diameter and extending 1.5 cm. in depth, was found at the site of constriction. The base of the ulcer was greyish-white, and extended for a distance of 0.7 cm. into the surrounding tissue. The pathological diagnosis was non-specific ulceration of the jejunum, with reticulum-cell hyperplasia of the regional lymph nodes.

The patient's postoperative course was uneventful for 7 days. On the eighth day the patient again complained of severe, burning, epigastric pain radiating through to her back. A Sippy diet, antacids, and vagal blocking agents seemed to control the pain, and an upper gastro-intestinal series on the twelfth postoperative day showed a normally functioning anastomosis, without evidence of obstruction or ulcer. The patient continued to improve, and was discharged on her twenty-first hospital day, August 27, 1952, tolerating an ulcer discharge diet.

The patient was readmitted to the hospital one week later, September 3, 1952, because of recurrent left-sided abdominal pain with radiation to the back. Additional complaints included constant nausea and anorexia, and a severe, watery diarrhea. Her weight had fallen to 88 pounds. There was moderately severe left lower quadrant tenderness with guarding. The initial 12-hour gastric aspiration indicated excessive hypersecretion and hyperacidity: volume, 3,170 ml.; free HCl, 86 clinical units; total free HCl, 272 mEq.; total acid, 92 clinical units (Fig. 2). One week later, while the patient was receiving an atropine derivative to its maximum dosage, the 12-hour volume measured 2240 ml., and contained 145.6 mEq. of free HCl. These findings were duplicated on consecutive studies,

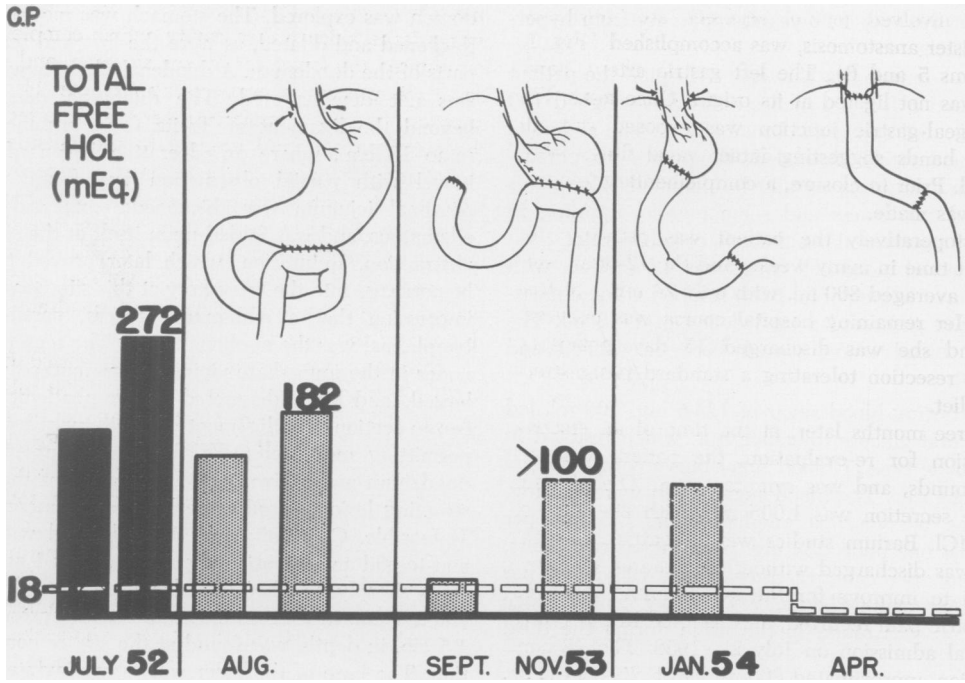

FIG. 2. Total mEq. of free HCl found in repeated 12-hour nocturnal gastric aspirations of Case 1 (C. P.), showing the effect of those operative procedures designed to reduce the gastric hypersecretion and hyperacidity. The normal value is indicated by the broken horizontal line.

Roentgenologic studies demonstrated a diverticulum-like projection with a narrow neck at the site of a partial constriction of the jejunum, several centimeters distal to the previous anastomosis. This was diagnosed as a solitary recurrent jejunal ulcer. Despite intensive antacid therapy, the patient's course became progressively worse, and a tender mass became palpable in the left upper quadrant. Fearing a jejunocolic fistula, re-operation was decided upon to control the excessive hypersecretion. Narcotics were required at intervals of less than two hours on the night preceding operation, suggesting an impending perforation.

At operation a large inflammatory mass was found in the jejunum just distal to the previous anastomosis, and firmly fixed to the under side of the transverse colon near its mesenteric attachment. The involved small bowel was separated from the transverse colon by sharp dissection through the base of a large recurrent jejunal ulceration; and having determined the absence of a communicating fistula, the involved jejunum, including the previous suture line, was resected and continuity established by a two-layer end-to-end anastomosis. Subtotal gastrectomy was considered, but the patient's weight of only 92 pounds indicated a more conservative procedure. A subdiaphragmatic vagotomy and a short loop iso-peristaltic gastro-jejunostomy were accomplished parallel to the greater curvature of the stomach and as close to the pylorus as possible (Fig. 1, Diagrams 3 and 4).

The resected portion of bowel measured 22 cm. in length, and contained multiple ulcerations. The largest of these began 1.5 cm. distal to the healed anastomosis, and measured 5.5 cm. x 3 cm. The ulcer was indurated and sharply defined, and had eroded through mucosa and muscularis.

Large volumes of gastric juice drained from the Levin tube immediately following operation. This fact, plus the recurrence of severe left upper quadrant pain on the third postoperative day, pointed toward the development of a marginal ulcer. The efferent loop functioned satisfactorily, with little or no gastric retention at 30 minutes. Although initial 12-hour gastric aspiration demonstrated some lowering of the gastric acidity, this was short-lived.

Roentgenologic studies were suggestive but not conclusive of a stomal ulcer. The patient's weight had fallen to 84 pounds. At operation, October 8, 1952, a large marginal ulcer was identified, which had penetrated deep into the traverse mesocolon. A 70 per cent subtotal gastrectomy, with removal

of the involved jejunal segment and retrocolic Hofmeister anastomosis, was accomplished (Fig. 1, Diagrams 5 and 6). The left gastric artery, however, was not ligated at its origin. Once again the esophageal-gastric junction was exposed and all fibrous bands suggesting intact vagal fibers were divided. Prior to closure, a complementary jejunostomy was made.

Postoperatively the patient was pain-free for the first time in many weeks, and the 12-hour aspirations averaged 800 ml. with only 24 mEq. of free HCl. Her remaining hospital course was uneventful, and she was discharged 15 days following gastric resection tolerating a standard postgastrectomy diet.

Three months later, at the time of an elective admission for re-evaluation, the patient weighed 105 pounds, and was symptom-free. The 12-hour gastric secretion was 1,005 ml., with 29 mEq. of free HCl. Barium studies were negative. The patient was discharged without medication, and continued to improve for the next month. However, epigastric pain recurred, and resulted in her fourth hospital admission on July 29, 1953. The 12-hour secretion approximated 800 ml., with 26.4 mEq. of free HCl. She had lost 12 pounds in weight since January, 1953, and a marked deficit in blood volume was noted. A course of intensive ulcer therapy was instituted, and the patient was discharged to her family physician.

The symptoms were controlled with therapy previously advised until October, 1953, at which time a marginal ulceration was demonstrated by roentgenogram. In November, 1953, she was admitted to her local hospital, where a transthoracic vagotomy (Fig. 1, Diagram 7) had failed to control her progressive symptoms or alter a positive Hollander test. The mEq. of free HCl exceeded 100 at the time of the 12-hour secretion studies (Fig. 2). One month later, the marginal ulcer was excised, additional stomach was removed, and continuity was restored by a gastroduodenostomy (Fig. 1, Diagrams 8 and 9). The postoperative course was stormy, and following an episode of chills and fever, a gastro-enterocutaneous fistula appeared, which drained varying amounts of gastro-intestinal secretions, and made electrolyte maintenance a difficult problem.

When transferred to University Hospital in February, 1954, her weight had fallen to 72 pounds. The patient's general condition improved, but the gastric fistula remained unchanged, and accordingly was approached surgically on April 2, 1954. The gastroduodenostomy appeared to have separated completely, except for one small area on the lesser curvature side (Fig. 1, Diagram 10). The open duodenum and gastric pouch communicated with a large, thick-walled cavity, which completely surrounded the lower end of the stomach, and any definitive procedure was considered out of the question. A large Pezzar catheter was inserted in the gastric pouch, and brought to the outside in an attempt to divert the acid gastric juice away from the ulcerated area. A smaller, but longer, catheter was placed in the open end of the duodenum for feeding purposes, and the cavity itself was packed with gauze. Prior to closure a large, walled-off abscess in the right lower quadrant was drained to the outside.

Drainage from the gastric pouch varied from 1625 ml. to 4750 ml., and averaged 3750 ml., in spite of the patient's taking nothing by mouth. Free HCl was present in the amount of 56 mEq./liter, and averaged 106 mEq. during each 12-hour period. The free HCl was neutralized with sodium bicarbonate, and all of the collected secretions were then returned to the gastro-intestinal tract by means of the duodenostomy. Two weeks later the patient suffered two successive massive gastro-intestinal hemorrhages, requiring 18 pints of whole blood to replace the loss. Continued bleeding necessitated total gastrectomy with esophago-duodenostomy, accomplished on April 14, 1954 (Fig. 1, Diagram 11).

On May 27, 1954, a duodeno-esophago-cutaneous fistula was demonstrated, which gradually increased in size, drained large amounts of bile and jejunal contents, and led to her ultimate demise June 7, 1954.

Significant autopsy findings included a generalized plastic peritonitis, with multiple localized abscesses. Gross examination of the initial stained sections from the tail of the pancreas disclosed a well-encapsulated nodule, measuring 1 cm. in diameter in the central portion of the gland (Fig. 3A). Several similarly encapsulated nodules were seen surrounding the major adenoma.

HISTOLOGIC DESCRIPTION OF PANCREATIC TUMORS*

Microscopic study of the pancreas showed several nodules of varying size. The larger ones were composed of hyaline fibrous tissue, in which small tumor cells could be found grouped into nests and separated by broad strands of stroma (Fig. 3). In the

* The authors are grateful to Dr. Emmerich von Haam, Professor and Chairman, Department of Pathology, Ohio State University College of Medicine, for his microscopic description of the tumors reported herein.

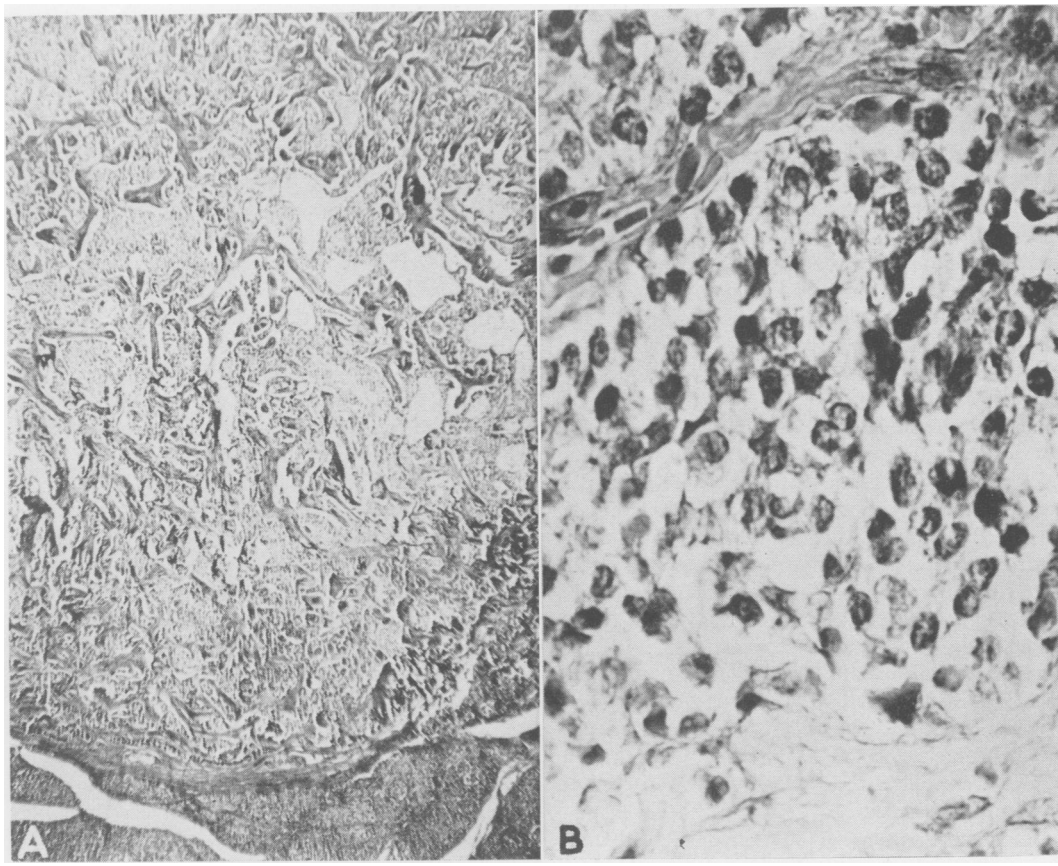

FIG. 3. Photomicrographs of pancreatic islet cell tumor in Case 1 (C. P.). (a) Low magnification showing characteristic fibrous stroma separating tumor cells into groups. Note the surrounding normal pancreatic tissue. Mallory tri-chrome; 13X. (b) High magnification showing typical tumor cells with an increased nucleo-cytoplasmic ratio. No granules are identified. Gomori technic; 460X.

smaller tumor nodules, some of which hardly exceeded the size of one of the oversized normal islands, the tumor cells formed trabecular patterns with scant stroma and only a few capillaries. The tumor cells were cuboidal to low columnar in shape, having a pale, staining nucleus containing diffuse chromatin and one to several small nucleoli. With the aldehyde-fuchsin-trichrome stain, the tumor cells showed a pale purple nucleus and a green cytoplasm. In some areas of the larger tumor nodules, a bluish tinged vaculoic fluid could be seen forming small pools between tumor cells. When compared with the normal islet cells, it appeared that the tumor cells were somewhat larger than the Beta cells, and that the cytoplasm showed definite greenish tinge without granulation. It was concluded that the pancreatic nodules were islet cell tumors of undetermined type, and did not contain secreting Beta cells.

Case 2. J. M., a 19-year-old single white female, was first admitted to University Hospital Emergency Room, Columbus, Ohio, on January 19, 1954, with the chief complaint of severe vomiting and abdominal pain for 15 hours. A tentative diagnosis of intestinal obstruction was made.

The patient had enjoyed good health until July, 1951, when she suffered unexplained upper abdominal pain. This pain continued intermittently until February, 1952, at which time she underwent a negative exploratory laparotomy and an incidental

appendectomy without relief of her symptoms (Fig. 4, Diagram 1). In July, 1953, the patient developed acute abdominal pain. The diagnosis of a perforated viscus was made. At laparotomy two separate jejunal ulcers, located 6 inches from the ligament of Treitz, were identified and closed primarily (Fig. 4, Diagram 2). In October, 1953, intestinal obstruction necessitated re-operation and lysis of adhesions (Fig. 4, Diagram 3). One month later a similar episode of obstruction was controlled by long tube suction. During the interval from July, 1951, to November, 1953, the patient lost 59 pounds from her original weight of 180 pounds.

At the time of physical examination the patient appeared acutely ill and complained of severe abdominal pain. Vital signs included: temperature, 100.4°; respiration, 24; pulse, 144; blood pressure, 100/80. The skin was dry and pale. There was considerable hirsutism of the face and neck. Only minimal abdominal distention was noted. Marked tenderness and some guarding were present throughout the upper abdomen, and no masses could be palpated. The patient's height was 5 feet 2½ inches, and she weighed 121 pounds.

Roentgenologic studies showed several loops of moderately dilated small bowel in the left upper quadrants without fluid levels. There was no evidence of free air. With a working diagnosis of recurrent high small bowel obstruction, Miller-Abbott intubation was instituted, and the appropriate parenteral fluids were given. On the following morning, 200 ml. of a thin barium mixture plus a similar amount of iced, normal saline was introduced into a long tube. The small bowel was slightly dilated and showed segmentation without obstruction. Barium was noted in the cecum within 45 minutes. Jejunal ulceration was not seen. With these findings, the long tube suction was discontinued.

The red count was 5.05 million and 16.1 Gm. of hemoglobin. RIHSA blood volume measurements indicated a total deficit of 1620 ml. The red cell mass was normal but the plasma volume was nearly 50 per cent below the theoretical normal. The total circulating plasma protein was 85.4 Gm. as compared to a normal of 173 to 231 Gm. A 12-hour gastric aspiration on January 23, 1954, produced a volume of 2800 ml., with 308 mEq. of free HCl (Fig. 5). The next day 2400 ml. containing 259 mEq. of free HCl was obtained. Tests for occult blood were negative. The prothrombin value was 65 per cent of normal. The fasting blood sugar was 102 mg. per cent.

A repeat upper gastro-intestinal series showed considerable hypersecretion, a possible duodenal ulcer in the apical portion of the duodenal bulb, and a sacculation behind the stomach, suggestive of jejunal ulceration. Coarseness and segmentation of the small bowel were again noted.

The blood volume deficit was corrected with whole blood transfusions, and on January 28, 1954, a subdiaphragmatic vagotomy, radical gastrectomy with fundusectomy and end-to-end gastroduodenostomy were accomplished in an attempt to control this tremendous gastric hypersecretion. The residual gastric pouch measured 6 cm. x 8 cm. (Fig. 4, Diagram 4).

The gross specimen of the removed stomach measured 26 cm. along its greater curvature, and 13 cm. along the lesser curvature. The rugal folds seemed more prominent than normal but no scarring or ulcer craters were demonstrated. Microscopic sections of the pyloric area, the antrum, and the fundus were interpreted as showing hyperplasia of the parietal cells. The muscular layers were thickened and fibrotic, and contained many scattered focal collections of lymphocytes.

The postoperative course was uneventful until February 7, ten days postoperatively, at which time the patient complained of precordial burning and high midline back pain, requiring narcotics for control. The 12-hour gastric aspirations showed a considerable reduction in both volume of secretion and acid, but still remained above normal. Just before discharge, the 12-hour volume was 570 ml. with a total free HCl of 28 mEq. (Fig. 5). All specimens were positive for occult blood. The patient's pain gradually subsided, and she was discharged on February 14, 1954, tolerating the standard postgastrectomy diet with little or no symptoms of dumping.

Within 24 hours after discharge she developed a severe, cramping, right upper quadrant pain which persisted until readmission on February 16, 1954. She had vomited twice, and the vomitus in one instance was bloody. The abdomen was not distended, bowel sounds were hyperactive, and a movable, sausage-shaped, tender mass in the right upper quadrant was interpreted as representing a duodenitis. This diagnosis was confirmed by roentgenogram. Intensive medical therapy, including milk and cream at hourly intervals, led to relief of her symptoms, and she was discharged on intensive antacid therapy.

The third hospital admission was 4½ months later, on July 14, 1954. Since discharge in February, she had suffered intermittent periods of vomiting, with mid-epigastric burning pain which radiated to the back. Medication and diet had been followed implicitly. In spite of these setbacks, she had been able to gain weight up to 147 pounds, and had returned to work. Routine laboratory data were within normal range. The Hollander test was interpreted to be positive for intact vagal fibers on

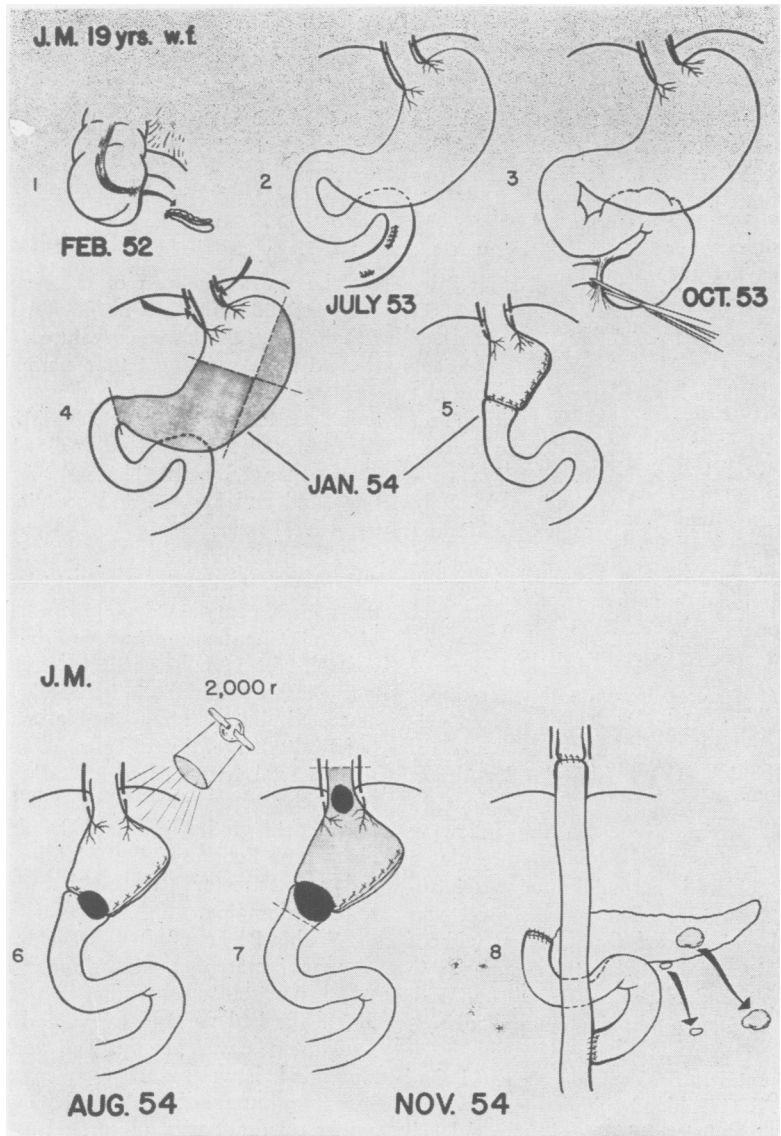

FIG. 4. Schematic representation of clinical course of Case 2 (J. M.), including operative procedures from time of initial symptoms through total gastrectomy. Complications of the primary jejunal ulcerations and sites of recurrent ulcer are indicated. Radiation of the gastric pouch is indicated in Diagram 6. The location of the pancreatic islet tumors excised at the time of total gastrectomy are shown in Diagram 8.

two occasions, with an increase of the mEq. of the free HCl from 45 to 64, and on a second trial from 31 to 65.5. In each instance a hypoglycemia below 50 mg. per cent had been attained.

While the patient was receiving vagal blocking agents, a 12-hour gastric aspiration again resulted in 2000 ml. of gastric juice, with a total of 32 mEq. of free HCl. Two days later, having received no medication for 36 hours, the patient's total volume was only 1260 ml., but the total free HCl increased to 74 mEq. A repeat study on July 19, 1954, resulted in 1500 ml., containing a total of 75 mEq. of free acid. Fasting blood sugars on four different occasions were 80, 78, 85, and 91 mg. per cent.

Fluoroscopy of the gastric pouch demonstrated a herniation of the fundus through an enlarged hiatal opening. The gastro-duodenostomy stoma functioned satisfactorily, but a small barium pocket

projecting from the greater curvature side suggested the possibility of an ulcer crater. There was marked coarsening and widening of the mucosal folds of the duodenum. Although her symptoms gradually improved during hospitalization, roentgen ray therapy directed to the small gastric pouch, using anterior and posterior ports with careful shielding of the ovaries, was undertaken in an attempt to control the persistent hypersecretion and to avert, if possible, the need for total gastrectomy. Arrangements having been made for the patient to receieve 100 r twice weekly for a total of 2000 r to the gastric pouch, she was discharged on July 24, 1954. Antacids and the ulcer diet were continued.

Recurrent nausea and progressive vomiting, which failed to respond to medication, resulted in her fifth hospital admission on August 28, 1954. Radiation therapy to the gastric pouch had nearly been completed, totalling 1900 r (Fig. 4, Diagram 6), when excruciating, burning epigastric pain proved unresponsive to medication, and necessitated continuous aspiration of the gastric contents for 48 hours. Residual tenderness over the right rib margin was thought to have resulted from radiation chondritis, and was relieved by intercostal nerve block.

The body weight on admission had fallen to 131 pounds. The initial 12-hour aspiration of 1250 ml. indicated some reduction in the excessive secretion of the stomach. The free HCl measured 42 clinical units, making a total of 21.5 mEq. The improvement, however, was only short-lived. Repeat studies 10 days later yielded a total volume of 1350 ml., with a total of 81.9 mEq. of free acid. The pH was 1.2. A 15-hour fast did not result in hypoglycemia. The patient was discharged on September 25, 1954, to be re-evaluated for possible total gastrectomy within one month.

On October 17, 1954, she was hospitalized for the sixth time within 9 months. The ulcer-like pain had been almost continuous, and vomiting occurred daily. The total volume of gastric secretion for 12-hour periods remained relatively low, varying from 325 to 695 Ml. Acid production, on the other hand, remained high, and the free HCl ranged from 49 to 94 mEq. per liter. The 4-hour glucose tolerance curve was normal. Urinary steroids showed slight elevations on occasion and osinophil counts continued at subnormal levels. Hirsutism was extensive and the face appeared to be moon-shaped. A repeat Hollander test resulted in an increased acidity greater than 20 clinical units, and seemed to indicate the presence of functioning vagal fibers.

Because of a possible functioning islet cell tumor with hyperinsulinism, the patient was fasted for 48 hours, but repeat blood sugars demonstrated no evidence of hypoglycemia (minimum 80 mg. per cent). During the fast the patient's symptoms markedly increased, and required narcotics for control of pain. Fearing perforation, an emergency gastro-intestinal study was done on the last day of the fast and demonstrated esophagitis, a gastro-esophageal ulcer, and a penetrating stomal ulcer at the gastroduodenal junction (Fig. 4, Diagram 7).

Total gastrectomy was then decided upon, and following several days of supportive parenteral therapy, the patient was scheduled for operation. While the lower esophagus was being freed for resection, a posterior penetrating esophageal ulcer just proximal to the cardia was identified. A 1¼ inch ulceration had practically replaced the posterior side of the gastroduodenal anastomosis. The gastrectomy having been accomplished, the duodenum could not be mobilized sufficiently to permit a Billroth I anastomosis, and continuity was established by a Roux-en-Y esophagojejunostomy (Fig. 4, Diagram 8). The adrenal glands were explored for tumor, but non was found; however, a generous biopsy of the left adrenal was taken. The pancreas was also inspected for an islet tumor, and two small nodules thought to be lymph nodes were excised from the anterior aspect of the tail of the pancreas. The removed specimen measured 9 cm. x 12 cm., and when opened showed prominent rugal folds (Fig. 6A). A 1.4 cm. ulcer was noted at the esophagogastric junction. The esophagus was thick and indurated, and felt almost like cartilage. The gastroduodenal ulcer measured 4 cm. x 3 cm.

Microscopically, the edges of the ulcers were necrotic and infiltrated with polymorphonuclear leukocytes. The necrosis extended through the entire thickness of muscularis. The gastric mucosa appeared normal. Section of the adrenal gland showed abundant lipid within the cortex, and was otherwise considered normal.

MICROSCOPIC DESCRIPTION OF PANCREATIC NODULE

The largest of the two nodules removed from the tail of the pancreas was composed of acinar masses of cuboidal to cylindrical cells, which showed an irregularly-oval nucleus containing finely diffused chromatin and one or several round to oval nucleoli (Fig. 6). The cells were distinctly outlined, and although the cytoplasm was mostly homogenous, it occasionally contained very fine stippling and irregular vacuoles. The acinar masses were separated by fibrous stroma carrying the blood supply. There was no evidence of accumulation of secretion. The tumor was sharply demarcated from the normal pancreas by a thin capsule-like layer of stroma which, however, in several places was penetrated by tumor cells. The pancreatic tissue re-

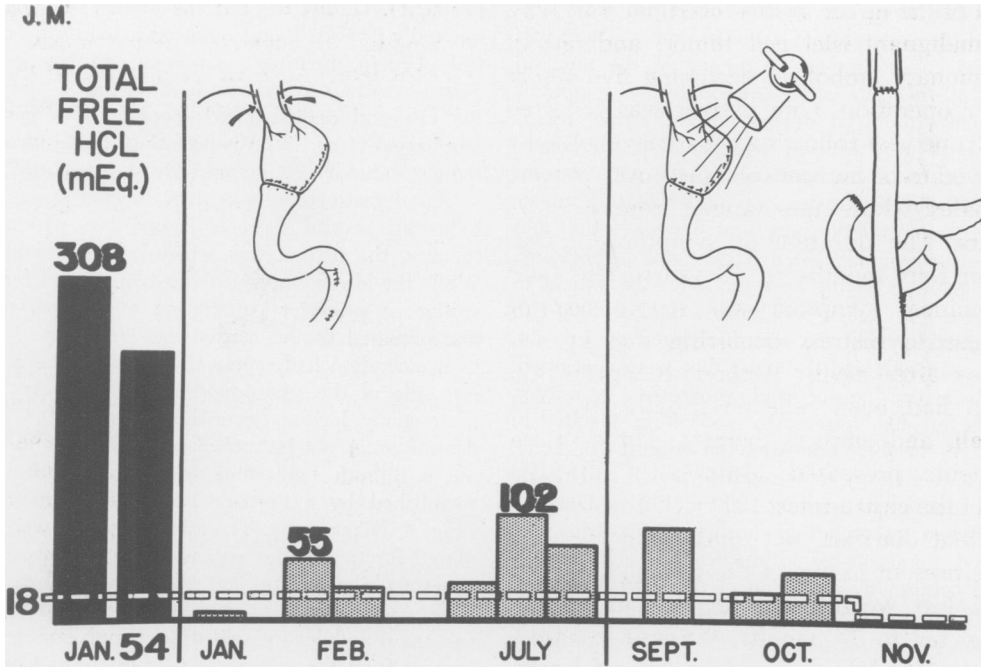

FIG. 5. Total mEq. of free HCl found in repeated 12-hour nocturnal gastric aspirations of Case 2 (J. M.), showing the effect of operation and radiation of the gastric pouch on gastric secretion and acidity. The normal value is indicated by the broken horizontal line.

moved with the tumor showed normal islands with many large Beta cells and no evidence of glandular pathology. With the Mallory stain groups of larger cells could be distinguished with more cytoplasm and a paler staining nucleus than other cell groups where the cells appeared smaller, with a bright, dense nucleus and a markedly increased nucleo-cytoplasmic ratio. The larger cells showed a distinct pale blue cytoplasm. No granules of any type could be distinguished.

The aldehyde-fuchsin-trichrome stain demonstrated normal Beta granules of the islet cells of the pancreatic tissue. No granules of any type were demonstrated in the tumor. It was concluded that the tumor represented an islet cell neoplasm with malignant characteristics, and one in which the cells were not of the secretory Beta-cell type.

The second and smaller nodule proved to be a lymph node containing similar-type cells, and was considered to represent a possible metastatic islet cell tumor (Fig. 6C).

The patient's convalescence was quite satisfactory, and she maintained her weight at 116 pounds up to the time of discharge, on her 15th postoperative day. Uropepsin values, which has been exceedingly high before operation, had fallen to zero.

Her course after leaving the hospital was complicated by a gradual stricture of the esophago-jejunal junction, and esophageal dilatation was started on an out-patient basis. On January 10, 1955, shortly after one of these dilatations, the patient complained of severe substernal pain and several hours later was admitted to the hospital with a perforation of the anastomosis into the right pleural space. The yellowish fluid obtained on thoracentesis was positive for bile, and pancreatic juice and a closed thoracotomy drainage was accomplished. The patient improved, and following a negative barium swallow, was once again started on oral feedings. Several days later sepsis became obvious, and an open thoracotomy was done for right-sided empyema. After a stormy postoperative period, the patient gradually improved and was discharged on February 15, 1955, able to tolerate a soft diet. Her weight, which had fallen to 99½ pounds, gradually increased to 109 pounds by April. At the present time the patient has no complaints but still requires regular dilatation of the esophago-jejunal anastomosis.

Although there may be others, four additional examples of pancreatic islet cell tumors without clinical or laboratory evidence of insulin production have been reported in patients with gastric hypersecretion and peptic ulceration.[2, 8, 9, 19] Three of the four patients are dead; one of recurrent ulcera-

tion of the upper gastro-intestinal tract; one of malignant islet cell tumor; and one of pulmonary embolism occurring five weeks after operation. One patient was reported well one year following the removal of what proved to be an islet cell adenoma. All were females, whose ages ranged from 40 to 74 years. The duration of symptoms ranged from four months to 12 years. The most prominent symptom was severe burning epigastric distress occurring one or two hours after meals. Without exception, the pain had been relieved intially by food, alkali, and empiric therapy. Three of the patients presented histories of bleeding from the gastro-intestinal tract. Severe intermittent diarrhea, not unlike that of C. P., was present in one of the four patients. All had lost weight, and the amount varied from ten to 37 pounds. Without exception there was laboratory evidence of gastric hypersecretion and hyperacidity, and peptic ulceration was demonstrated in all at subsequent operation. Three of the ulcers were found in the second, and one in the third portion of the duodenum.

Indications for operation included symptoms in three and the presence of an abdominal mass in the left upper quadrant in one. In the latter, a 6 cm. x 8 cm. encapsulated tumor was removed from the junction of the tail and body of the pancreas.[19] A gastro-enterostomy was then accomplished to by-pass the ulcer in the second portion of the duodenum. The tumor consisted of broad sheets of tumor cells, showing no alpha or beta granules with Gomori's technic. Vacuoles were prominent in the cytoplasm. Mitosis and invasion of the surrounding pancreatic tissue indicated malignancy. In this case, the authors suggested that the tumor was composed of a delta-type islet cell.

It is significant that the severe, ulcer-like gastric distress present for many years subsided completely for three years and then recurred. One year later laparotomy showed recurrent tumor, and the patient expired following a massive hematemesis two months later. Autopsy demonstrated the recurrent islet cell carcinoma with generalized metastasis, a chronic duodenal ulcer, and infarction of the proximal jejunum. In this instance peptic ulceration was apparently controlled following removal of the islet tumor, and recurred with the appearance of metastasis. No clinical evidence of hyperinsulinism was found.

A second patient underwent subtotal gastrectomy for obstructing duodenal ulcer.[9] A biopsy of a pancreatic tumor and regional nodes showed a malignant islet cell with blood vessel invasion and metastasis to regional lymph nodes. Once again, there was no clinical or laboratory evidence of insulin secretion. This patient died at home five weeks later of a pulmonary embolus.

The third patient with ulcer-like epigastric pain of two years' duration accompanied by vomiting and tarry stools and with gastric hypersecretion underwent a pancreatico-duodenectomy for an indurated mass in the third portion of the duodenum.[8] The removed specimen contained a large ulcer crater, in addition to a small islet cell carcinoma of the head of the pancreas. The patient expired on the 27th postoperative day of a perforated stomal ulcer, and at autopsy two small islet cell adenoma were identified. Hyperinsulinism had been considered a possible factor in the excess acid production, but no laboratory evidence of hypoglycemia had been uncovered.

The last patient presented ulcer-like symptoms, diarrhea, and an 18-pound weight loss over a four-month period.[2] High gastric acidity was noted following an Ewald test meal. Roentgen showed a large dilated duodenal bulb with constriction of the second portion of the duodenum. At operation a well-encapsulated tumor, measuring 6.6 cm. in diameter, was removed from the head of the pancreas, and the duodenum was not disturbed. The epigastric dis-

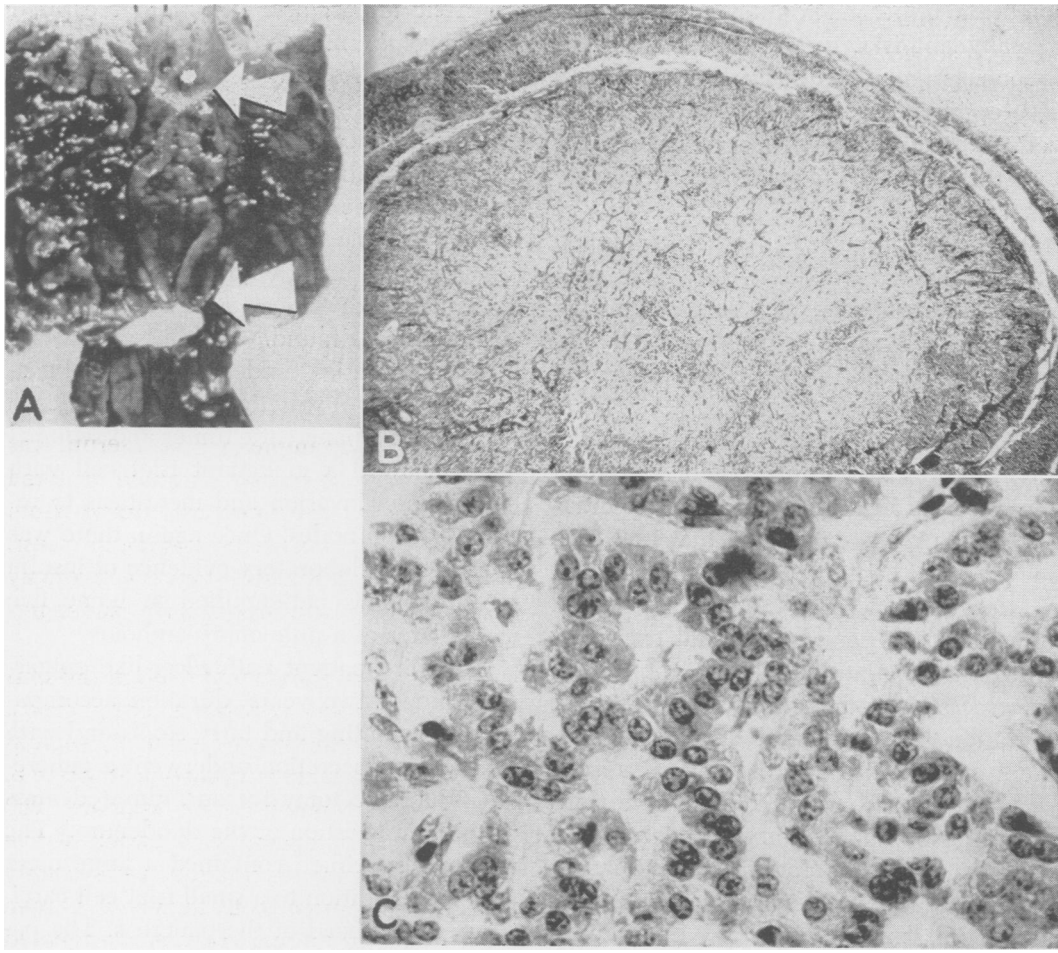

FIG. 6. (A) Gastric remnant following subtotal gastrectomy and fundusectomy in Case 2 (J. M.) showing the gastro-esophageal and gastroduodenal ulcerations. Photomicrographs of the pancreatic tumor removed at the time of total gastrectomy are shown in (B) and (C). (B) Low magnification of islet tumor in Case 2 (J. M.), showing the tumor sharply demarcated from normal pancreas by a thin capsule of stroma which is penetrated in several places with tumor cells. Mallory tri-chrome; 11X. (C) High magnification of tumor in Case 2 (J. M.), showing the irregular oval nucleus containing finely diffused chromatin and one or several round and oval nucleoli. The cytoplasm contains fine strippling and irregular vacuoles. No granules of any type are seen. Aldehyde-fuchsin-trichrome stain; 375X.

tress and diarrhea were controlled, and the patient gained 28 pounds during the next year. Microscopic study of the tumor showed polyhedral cells with round to oval nuclei interspersed between bands of collagenous tissue. Red staining, or alpha cell granules, were noted in some of the tumor cells with Gomori's stain.

Three additional patients with similar histories of recurrent peptic ulceration, excessive secretion of acid gastric juice, and eventual demonstration of islet cell carcinomas have been called to our attention by Drs. Jenkins, Moyer, and Bernard.[11, 14]

The simultaneous occurrence of islet cell adenomas in each of nine patients with primary duodenal or jejunal ulcers, or secondary gastro-jejunal and gastro-duodenal ulcers associated with great hypersecretion and hyperacidity, lends support to the con-

cept of an ulcerogenic factor of pancreatic origin as suggested by Poth.[15] This concept was based on the observations by Dragstedt[4] and Elman[6] that spontaneous duodenal ulceration nearly always results from complete diversion of the external pancreatic secretions from the duodenum, while ulceration rarely (1.7 per cent) occurs following total pancreatectomy.[5] This led to the postulate that some intrinsic factor of the pancreas not related to its external secretions might have an influence on ulcer formation, since the external alkaline pancreatic secretion had been lost in either instance.[16]

The increased gastric secretory response to hypoglycemia implicates insulin.[1] Furthermore, sustained insulin hypoglycemia resulting from injection of commercial insulin favors the development of peptic ulcer in experimental animals.[17] This, however, is not the case in patients with chronic and severe hypoglycemia resulting from insulin-producing islet cell tumors of the pancreas. With two exceptions co-existent ulcer has not been reported, and in one of these the ulceration failed to improve following removal of the islet cell tumor.[10] The second exception resembles the patients reported here, inasmuch as multiple islet cell tumors were found in association with duodenal ulcer and its complications, together with adrenal hyperplasia.[3]

The isolation of a hyperglycemic-glycogenolytic factor (glucagon) from commercial insulin[12, 21] raised the question as to whether experimental insulin ulcerations are actually due to hypoglycemia, or rather to some hormonal action of glucagon.[18] This substance is secreted from the islets of the pancreas[7] and has been termed the antagonist of insulin, in that it promotes a breakdown of glycogen in the liver, and in turn raises the blood sugar.[13]

It seems attractive to speculate that the islet cell tumors in these nine patients might have been secreting excessive amounts of glucagon or some other substance capable of exciting gastric secretion. Since tumor cells had been found in one of the peripancreatic lymph nodes at the time of J. M.'s total gastrectomy, it seemed likely that the patient still harbored functioning tumor tissue. The patient's serum, therefore, was studied for the presence of some undetermined ulcerogenic factor, possibly glucagon.

Glucagon had previously been demonstrated to be a protein which could be identified and isolated from commercial insulin preparations by paper electrophoresis;[20] consequently, a sample of J. M.'s serum was obtained for such studies. It should be noted that the initial specimen was drawn from the patient at a time of maximum stress, namely, just prior to open thoracotomy drainage of an extensive and life-endangering empyema.

Separation of the patient's serum proteins was accomplished by paper electrophoresis. During a preliminary experiment, separation into six fractions occurred at pH 8.6, using barbitol buffer while applying 200 volts at 15 millamperes for a period of five hours. Five of the six fractions were readily identified as normal constituents of human serum. The additional fraction, designated as "fraction 5" by its position on the strip, had less mobility than gamma globulin, and was not present in normal serum.

Purified glucagon mixed with serum has electrophoretic characteristics identical to those of this unidentified fraction. Specimens of the patient's serum were applied repeatedly to two pairs of parallel paper strips for simultaneous electrophoresis. One strip from each pair was stained with bromphenol blue dye for identification of the fractions, and then discarded. The alternate strips were then cut in areas corresponding to six fractions. Each of the six fractions was then eluted from the paper sections with normal saline, dialyzed to rid the material of buffer solution, lyopholyzed, and the residual material dissolved in normal saline.

The hyperglycemic activity of each fraction was assayed in anesthetized cats by noting alterations in blood sugar after intravenous injection. Blood sugar levels were determined at five- to ten-minute intervals for a period of one hour after injection. Fractions 1 through 4 were relatively indifferent. Hyperglycemic activity was found in both of the remaining fractions. A moderate hyperglycemia (98 mg. per cent to 182 mg. per cent) was observed with fraction 6, and a marked rise in the blood sugar (96 mg. per cent to 240 mg. per cent) occurred following the injection of fraction 5. Repeat studies on a specimen obtained after the patient's recovery from the empyema, however, failed to show either the abnormal electrophoretic pattern or the hyperglycemic activity. The inability to duplicate these findings is discouraging. However, intermittant secretion from tumors of endocrine origin is not an uncommon finding, and necessitates repeated examinations of our patient's serum.

The electrophoretic isolation of an abnormal protein with electrophoretic properties identical to glucagon from the blood serum of a patient (J. M.) harboring an islet cell tumor and under stress, and the subsequent demonstration of its hyperglycemic properties by biological assay, suggests that the material in question was identical with, or at least similar to, the hyperglycemic-glycogenolytic factor of the normal pancreatic islet cell. In addition, it once again raises the question of the possible role of this factor in the stimulation of gastric secretion. Failure to control the hypersecretion by complete vagotomy and high subtotal resection in both reported patients (J. M. and C. P.) has already pointed toward a peripheral and in turn hormonal or chemical stimulation of the gastric glands. Since both the cephalic and the antral phases of gastric secretion had been eliminated, this postulated mechanism must act directly on the secretory element.[7] Studies of the effect of glucagon on gastric secretion in the human and experimental animal have been initiated, but to date sufficient data is not available for interpretation.

It would seem that a heretofore unrecognized islet cell tumor of the pancreas with an ulcerogenic potential must be considered in certain atypical cases of peptic ulcer disease. The clinical manifestations of this tumor are in contrast to those of the insulin-producing type, and constitute a diagnostic triad which includes:

1. The presence of primary peptic ulceration in unusual locations, *i.e.* second or third portions of the duodenum, upper jejunum, or recurrent stomal ulcers following any type of gastric surgery short of total gastrectomy.

2. Gastric hypersecretion of gigantic proportion persisting despite adequate conventional medical or surgical therapy.

3. The identification of non-specific islet cell tumor of the pancreas.

Therefore, the surgeon presented with the problem of controlling recurrent marginal ulceration or atypical primary ulceration should not overlook the possibility of an islet cell tumor of the pancreas. A careful search for individual tumors or even resection of the body and tail of the pancreas might well be considered in the rare instance before subjecting the patient to total gastrectomy as a final, heroic means of controlling the acid factor.

SUMMARY

1. Two instances of primary non-specific jejunal ulcers associated with marked gastric hypersecretion and hyperacidity have been studied. Recurrent ulceration followed standard surgical therapy in both cases, and necessitated total gastrectomy.

2. In each patient, non-specific islet cell tumors of the pancreas were eventually found.

3. Four additional similar cases found in the literature are reviewed.

4. An ulcerogenic humoral factor of pancreatic islet origin is postulated.

5. Theoretical reasons are given for implicating the hyperglycemic-glycogenolytic factor of the pancreas (glucagon).

6. In the one living patient available for study an electrophoretic analysis of the patient's serum demonstrated a protein fraction with mobility characteristics similar to those of glucagon. This fraction, not found in normal serum, elicited a hyperglycemic response in experimental animals.

7. A clinical entity consisting of hypersecretion, hyperacidity, and atypical peptic ulceration associated with non-insulin-producing islet cell tumors of the pancreas is suggested.

ACKNOWLEDGMENTS

The purified glucagon used in the studies described was generously supplied by Dr. W. R. Kirtley of The Eli Lilly Laboratory.

The electrophoretic studies described in this report were made under the direction of Dr. Walter Frajola, Director of The Herman A. Hoster Research Laboratory at Ohio State University.

The authors wish to thank Dr. G. Gomori for his interest and assistance in the staining of the tumors described, and also Dr. Richard Moore, Mrs. Margaret Murray, and Miss Theresa Chang for their assistance in the laboratory studies presented.

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