Ulcerogenic Tumor of the Pancreas *

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IN 1955, Zollinger and Ellison reported two cases demonstrating a new clinical entity, the salient feature of which was a fulminant ulcer diathesis.[32] The triad of unrelenting ulcer, gastric acid hypersecretion, and a non-beta islet adenoma of the pancreas was postulated as representing a clinical complex which was quite rare but very definite in those cases encountered. The ulcer often occurred in unusual sites and was stubbornly resistant to conventional medical or surgical therapy. An extensive review of their autopsy material by the original authors revealed additional previously unrecognized cases which were subsequently reported.[8] Numerous widely distributed isolated cases began to be recorded.[1, 4, 7, 11, 12, 15, 19, 20, 23, 29] Now some six years later, although they continue to be rare, between 75 and 100 cases have been described, many demonstrating additional aspects of this syndrome.[31]

Although the diagnostic triad of recurrent ulcer, acid hypersecretion and noninsulin producing islet tumor has continued to be the essential feature of this condition, certain variations have been noted as further information has become available. As accumulated reports have been assimilated it has become increasingly apparent that many of these tumors, although not conforming *histologically,* conduct themselves *clinically* as malignant neoplasms, metastasizing quite frequently.[2, 8, 16, 31, 33, 34] These secondary tumors are usually functional. It has also become evident that in patients with this ulcer diathesis nothing less than total gastrectomy is efficacious in eliminating recurrent ulcers, the complications of which have often proved lethal.[8, 31, 33, 34] Initially total pancreatectomy, an even more serious procedure, was performed, but most of the patients continued to experience ulcer difficulties inasmuch as they still received stimuli from the extrapancreatic tumors. Furthermore, the maintenance of pancreatectomized patients often has been difficult, so that total gastric resection, unsatisfactory as it may be, has evolved as the procedure of choice.[31] Some patients have been reported in whom intractable diarrhea [4, 23, 24, 26, 28] was the dominant symptom, occasionally resulting in severe electrolyte disproportion; and in others overt steatorrhea was the striking clinical feature.[7, 17] When it was recognized quite early that conventional medical and surgical therapy was ineffective, total vagotomy and even irradiation therapy to the fundic glands was employed. This, too, failed abysmally to stem the prodigious acid production.[31, 34]

Recently some doubt has been cast as to the existence of this syndrome.[35] Wermer [30] and others [10, 18, 27] have postulated that this is but a facet of a multiple glandular problem often involving the pituitary, the parathyroids or even the adrenal and thyroid glands. There is no doubt that in an occasional patient this is true, but the pancreatic ulcerogenic tumor does occur independently of any associated polyglandular disorder. In approximately 10 per cent of the cases reported diffuse adenomatosis involving certain islet cells has been noted in the absence of a specific pancreatic tumor.[26, 34] Although predominantly non-beta cell, and hence noninsulin producing, a few

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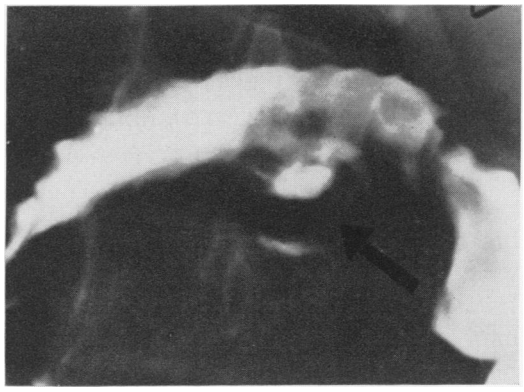

FIG. 1. Photograph of oblique x-ray study showing large posterior duodenal ulcer.

mixed tumors with hypoglycemia, as well as the ulcer tendency have been described.[16]

The precise etiologic agent elaborated by these tumors and thus responsible for the fulminant ulcer diathesis has not been isolated.[31-34] It has been demonstrated, however, that a substance far more potent than gastrin in the production of acid in experimental animals is produced.[13, 16] Initially, it was thought that this was a material resembling glucagon, the insulin antagonist, but at the present time this seems unlikely.[3, 21, 25, 31] Gregory *et al.*,[13] of Liverpool, first reported the isolation of a gastrin-like substance from a pancreatic tumor in a case of the Zollinger-Ellison syndrome. These investigators have more recently noted a similar finding in an additional patient from Cape Town, South Africa. The substance was found in both the primary and secondary tumors from a fatal case in a Bantu woman.[14, 16]

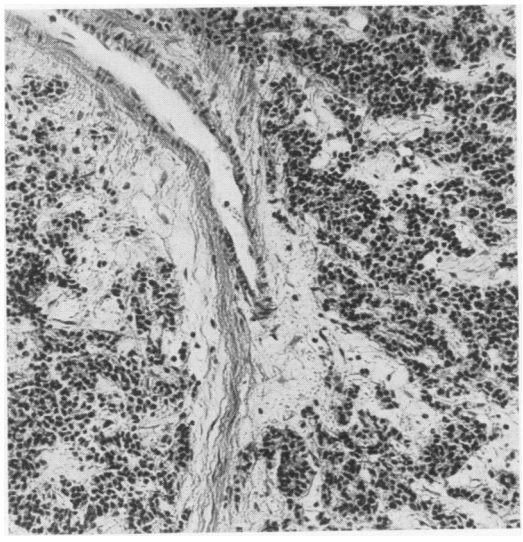

FIG. 2. Photomicrograph (low power) showing section of pancreatic tumor.

The report of a single case is prompted by the rarity of this condition plus its interesting ramifications. Particularly tantalizing is the possible role of the pancreas in the etiology of peptic ulceration in general. This latter concept is not original, having been postulated by others.[5, 6, 9, 21, 22] This apparently is the youngest patient in the literature demonstrating the rather classical triad described by Zollinger and his associates. Furthermore, extracts from a metastatic peripancreatic tumor in this patient have been found to incite a vigorous acid response in experimental dogs with Pavlov pouches.

Case Report

C. S., a white 15-year-old boy was first admitted to the Norfolk General Hospital on April 14, 1958, for the investigation of nausea, vomiting, and diarrhea of intermittant character of five-month duration. Approximately a week before admission he had begun to have burning colicky epigastric pain and had noticed tenderness in the same area. There was no history of hematemesis or melena. On admission the physical examination was totally negative except for slight tenderness in the epigastrium.

Laboratory work done on admission was not revealing. The urinalysis was negative. The hemoglobin was 16.6 Gm., 112 per cent and the white blood cell count 9,550 with a normal differential count. The serologic test was negative as was the quantitative van den Bergh. The stool examination, however, was slightly positive for occult blood. On April 15, an upper gastro-intestinal x-ray examination showed a slight deformity of the duodenal bulb without definite evidence of an ulcer niche. This examination was unsatisfactory and it was repeated on the following day. A large active duodenal ulcer was found in the mid-portion of the bulb on the second examination (Fig. 1). The ulcer crater measured 1.0 cm.

in diameter and there was marked edema surrounding it. The remainder of the upper gastrointestinal x-ray study was negative. The patient was started on a strict medical program by his family physician and was discharged from the hospital on April 21, 1958.

On April 25, four days after having been discharged on a conservative ulcer program, the second hospital admission for this patient became necessary. This was occasioned by the development of hematemesis. Shortly before entering the hospital he had vomited old blood. Otherwise there had been no change in his condition since discharge. Physical examination revealed mild shock, the blood pressure being 96/54 and the pulse 120. He was cooperative and coherent but pale. There was still tenderness in the epigastrium. The temperature was normal, the urinalysis negative, and the initial blood count was 14.4 Gm. or 96 per cent. The white blood cell count was 15,600 with 81 per cent polymorphonuclear neutrophiles. He obviously was bleeding from his duodenal ulcer. A transfusion of 500 cc. of blood was given on admission. Emesis of bright red blood occurred several times subsequently during the day. When this ceased and general improvement ensued feeding was begun on the following morning. Improvement was only temporary, however, and the tachycardia persisted. By nightfall the hemoglobin level had dropped to 65 per cent, 9.7 Gm. and further blood transfusions were given. During that night the rapidity of bleeding gradually increased and a continuous transfusion was administered. Despite this, however, the patient's pulse rate continued to increase, his hemoglobin and hematocrit persistently dropped, and it became apparent that emergency operation was indicated.

Early on the morning of April 27, under endotracheal anesthesia, the abdomen was explored and a huge posterior ulcer located just distal to the pylorus was found. An open artery, obviously a tributary of the gastroduodenal, was noted in the base of the ulcer. This spurted blood profusely when the clot filling the crater was removed. There was some contiguous induration of the head of the pancreas. A second lesion of considerable interest was detected. This was a mass 5.0 cm. in diameter lying in the pancreas on the superior margin at about the junction of the head and body. It was surmised that this represented a Zollinger-Ellison tumor and it was believed important to resect it as well as to do a high subtotal gastrectomy.

A gastric resection of the Billroth II type was carried out removing approximately 75 per cent of the stomach. The duodenum was closed snugly,

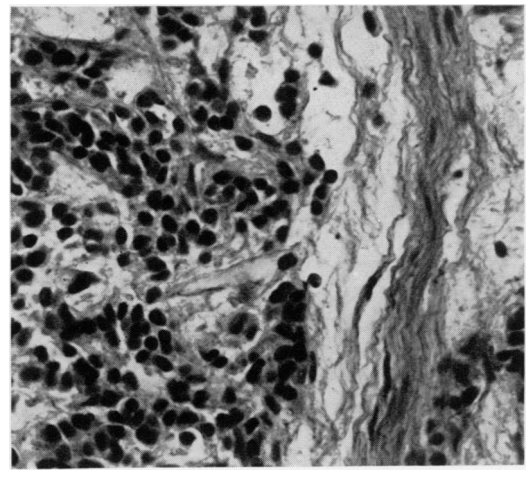

FIG. 3. Photomicrograph (high power) showing section of pancreatic tumor.

and an antecolic, short-loop gastrojejunostomy effected. It was necessary to leave the deeply situated ulcer base *in situ* in the head of the pancreas. The patient's condition was excellent during this procedure. The mass lying within the pancreas was then easily removed, mainly by enucleation, as a definite cleavage plane was present. No other masses were seen or felt at this time. The liver was normal as were the retroperitoneal lymph nodes.

Pathologic examination of the resected stomach

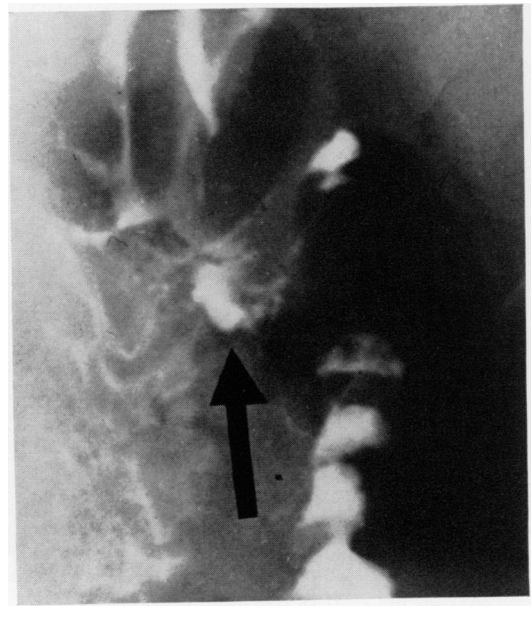

FIG. 4. Photograph of x-ray demonstrating the initial jejunal ulcer.

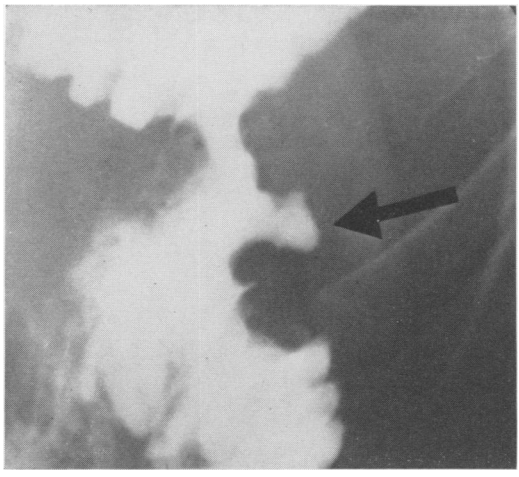

FIG. 5. Photograph of x-ray showing the second large jejunal ulcer. This subsequently healed following transthoracic vagotomy.

and pylorus revealed multiple superficial gastric erosions, a duodenal ulcer, and moderate gastritis. The pancreatice tumor was found to consist of neoplastic islet cells which grew in nests and at numerous points resembled exaggerated islets of Langerhans (Fig. 2, 3). The cells were small but of uniform size with scant cytoplasm and nuclei of equal staining quality. In some areas there was a departure from the well-circumscribed pattern and here the cells grew in solid cords infiltrating the supporting stroma. About the periphery of the lesion was a zone of compressed fibrous tissue and large numbers of lymphatic follicles. Vascularity was particularly pronounced in some areas

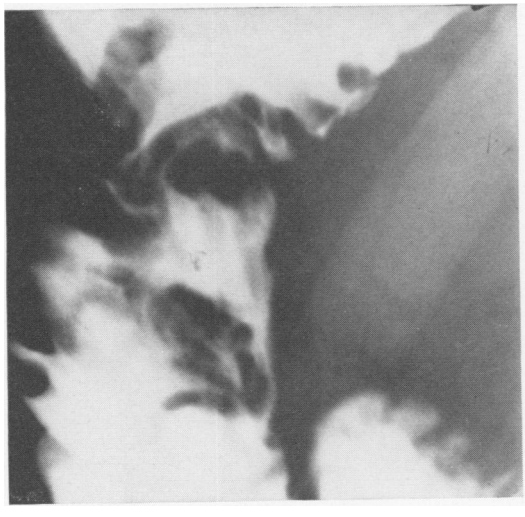

FIG. 6. Photograph of x-ray demonstrating evidence of healing of second marginal ulcer after transthoracic vagotomy.

and there was an occasional area of necrosis. Scattered individual cells were noted occasionally in the stroma. No normal pancreatic tissue was present. The neoplasm did not have a true capsule and areas of neoplasm were seen extending to the line of excision. The neoplastic tissue was well differentiated. Subsequent specific staining revealed the tumor to be made up predominantly of alpha and delta islet cells. No beta cells were seen.

The patient's postoperative course was uneventful and he was discharged from the hospital on the eighth postoperative day in excellent condi-

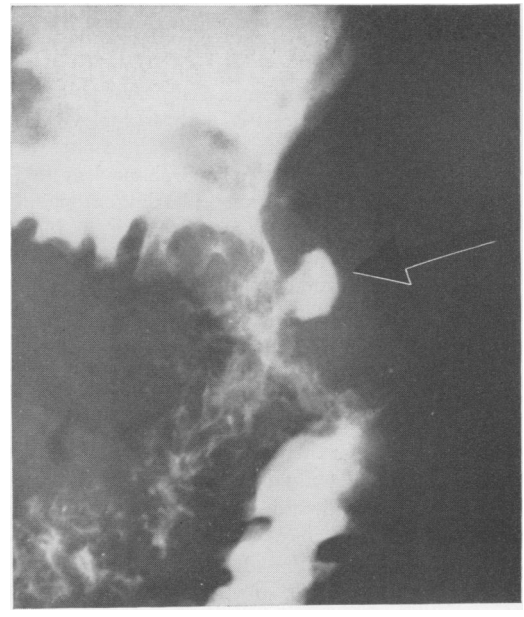

FIG. 7. Photograph of x-ray study demonstrating the third jejunal ulcer.

tion, tolerating a postgastrectomy diet unusually well.

The third hospital admission occurred 16 months later on August 5, 1959. The patient had remained symptom-free until approximately three and one-half hours before admission when he suddenly vomited a large quantity of bright red blood and passed a large, bloody, liquid stool. On admission he was quite pale, the pulse was 100, and the blood pressure 90/70. His admission hemoglobin was 12 Gm. or 80 per cent with 8,200 white blood cells and 70 per cent polymorphonuclear neutrophiles. A transfusion of 1,000 cc. of blood was given and over the next two days the bleeding spontaneously ceased. A diet was begun and on August 11, another gastro-intestinal x-ray examination revealed what was interpreted as a large marginal ulcer on the jejunal side of the

previous anastomosis (Fig. 4). It was believed further operation was mandatory and that it should include infradiaphragmatic vagotomy, resection of the jejunal ulcer, and construction of a new anastomosis. On August 15, the abdomen was re-explored under endotracheal anesthesia. At operation numerous adhesions were found over the upper abdomen with a large jejunal ulcer approximately 1.5 cm. distal to the anastomosis on the posterior jejunal wall. This was surrounded by a violent inflammatory reaction and was rather intimately attached to the transverse colon, although no fistula had yet occurred. Marked edema was present throughout this entire area. An infradiaphragmatic vagotomy was performed and the previous gastrojejunostomy taken down. A segment of jejunum approximately four inches long containing the ulcer was then resected and an end-to-end anastomosis carried out. A new gastrojejunostomy was created attaching the jejunum to the small residual gastric pouch distal to the jejunojejunostomy. The patient withstood the procedure well.

Pathologic examination revealed a jejunal ulcer and segments of the vagi. The patient's course was uneventful. He was discharged from the hospital on August 23, in excellent condition.

Nine months later on June 14, 1960, the fourth hospital admission was required for this young patient. He had remained asymptomatic following his last operation until two days prior to this admission, at which time he had become faint and had noticed tarry stools. On admission the hemoglobin was 78 per cent or 11.1 Gm. with a white blood cell count of 16,200, predominantly polymorphonuclear cells. His blood pressure was 100/60 and his pulse 80. He had an essentially normal course during the day of admission, but again became nauseated and vomited profuse bright red blood on several occasions, during the first hospital night. Blood transfusions were started. A tube was placed in his stomach and attached to suction. Decreasing amounts of old blood were evacuated over the next several days. Bleeding then ceased, and a dietary program was instituted. X-ray studies obtained on June 21 demonstrated a jejunal ulcer approximately 1.5 cm. in depth on the proximal side of the anastomosis just above the stoma (Fig. 5).

Further laboratory investigation revealed the

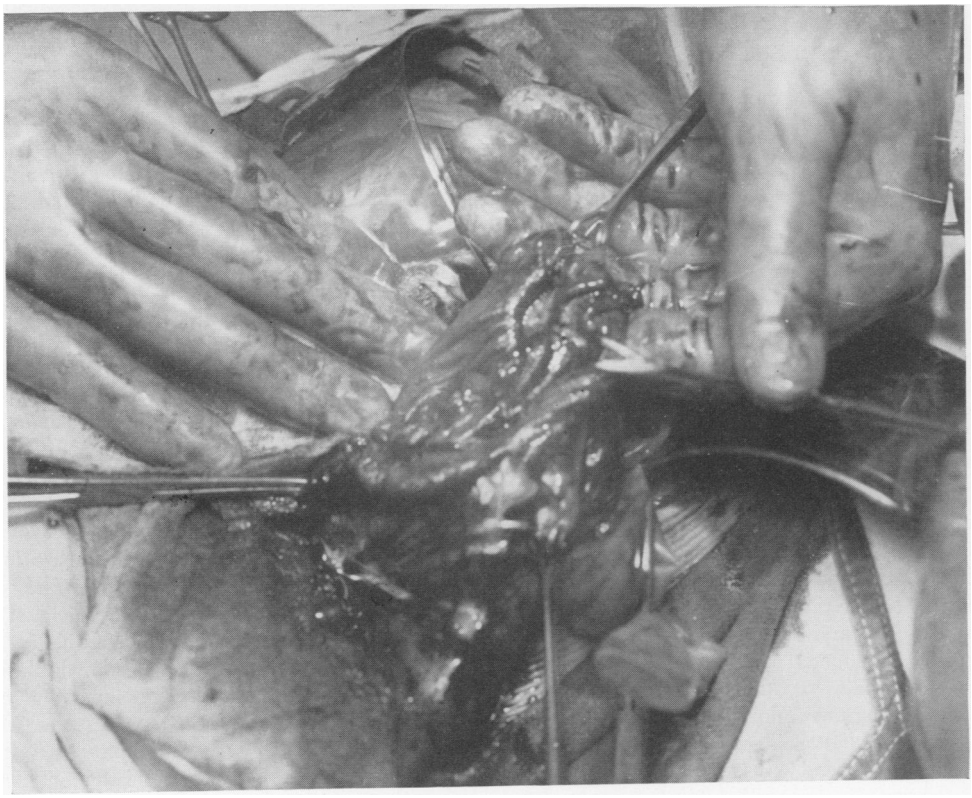

FIG. 8. Photograph made at operation showing third marginal ulcer. The jejunum has been opened.

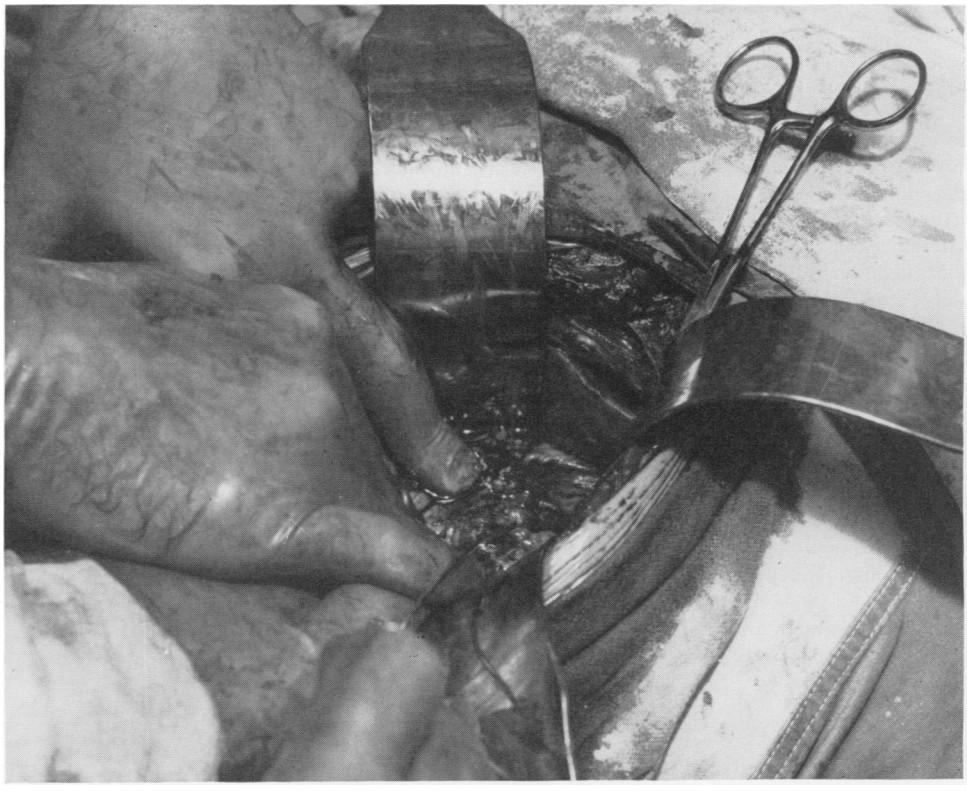

FIG. 9. Photograph made during operation demonstrating irregular nodular secondary peripancreatic tumors. The probe indicates several of these tumors.

blood calcium and phosphorus to be normal. However, a Hollander insulin test showed an extremely high total hydrochloric acid of 234 degrees and the blood sugar was carried down to 43 mg.%. This markedly positive Hollander insulin test suggested marked vagal activity.

On the possibility that the patient still had active vagal stimulation a transthoracic bilateral vagotomy was performed under endotracheal anesthesia on July 1.

The patient's postoperative course was smooth and he was discharged from the hospital in good condition on the seventh postoperative day. The segments resected from the two vagi were confirmed as nerves by the pathologist.

The fifth and most recent hospital admission of this patient occurred on September 4, 1960. In the two-month interim he had done quite well and had gained 15 pounds. An x-ray study one month after transthoracic vagotomy showed the previously noted marginal ulcer to have disappeared (Fig. 6). Dr. Robert Zollinger had been contacted in the meanwhile and gave most enthusiastic and helpful advice. He stated that in his experience a total gastric resection would be required in order to eliminate the profound ulcer diathesis, and he recommended this procedure. The patient, however, had remained asymptomatic and it was thought advisable to postpone this radical procedure as long as possible.

Shortly before entering the hospital the patient developed hematemesis, faintness and melena. On admission his blood pressure was 100/50 with a pulse of 86. A hemogram showed a hemoglobin level of 11 Gm., 79 per cent, and a white blood cell count of 10,000 with a normal differential. The external evidence of bleeding disappeared rather promptly with this episode but his hemoglobin continued to decrease and he was given several transfusions of whole blood. A Hollander insulin test showed no particular increase in acid at this admission but a gastro-intestinal x-ray study on September 6 demonstrated a large jejunal ulcer lateral to the primary anastomosis (Fig. 7).

Laboratory studies revealed normal blood sodium, potassium, chloride, calcium, and phosphorus. The serum protein was 5.7 mg.% with an albumin of 4.13 and a globulin of 1.4. The blood volume was 4,492 cc. Stool examination was positive for blood.

After adequate transfusion therapy had restored the hematocrit to normal the abdomen was

again explored on September 10, 1960, under endotracheal anesthesia. At this time massive adhesions were found to engulf the entire upper abdominal cavity. A huge marginal ulcer approximately 1.5 cm. in diameter and depth was found on the distal posterior jejunal side (Fig. 8). The liver was normal. Exploration of the pancreatic region revealed numerous retroperitoneal and peripancreatic masses ranging up to 4.0 to 5.0 cm. in diameter (Fig. 9). One particularly large one was palpated along the right renal vessels. Several accessible smaller masses were removed (Fig. 10). The residual gastric pouch was resected as well as the segment of jejunum containing the ulcer. The spleen was removed because of troublesome bleeding from the vasa brevia. The tail of the pancreas was resected also for histomorphologic study. The jejunum was anastomosed end-to-end at the site of resection for the ulcer. An esophageojejunostomy, end-to-side was then performed utilizing a Roux-en-Y, the distal end of the divided bowel was closed and an anastomosis between the esophagus and jejunum created approximately 5.0 cm. distal to the blind end of the small intestine. An end-to-side enteroenterostomy was carried out between the afferent and efferent loops. The patient's postoperative course was uneventful and he was discharged from the hospital seven days later in superb condition and tolerating his diet well.

Pathologic examination of the removed tissue revealed a marginal jejunal ulcer and an islet cell tumor from the peripancreatic region similar to the original pancreatic mass. Specific staining again showed absence of beta cells. Because of the sites of these secondary tumors, the pathologist believed these represented metastases, although there were still no malignant characteristics histologically. Sections of the stomach, jejunum, tail of the pancreas, spleen, and a peripancreatic tumor were sent to the laboratory of Dr. Robert Zollinger at Ohio State University for study and biologic assay. Extracts from the secondary tumor were found there to incite a vigorous acid response in Pavlov pouch dogs (Fig. 11). This reaction was

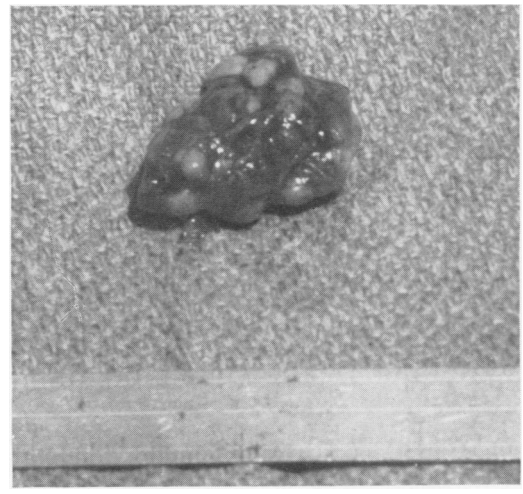

FIG. 10. Photograph of a secondary peripancreatic tumor (removed at the last operation). Extracts of this mass were made for injection into experimental animals.

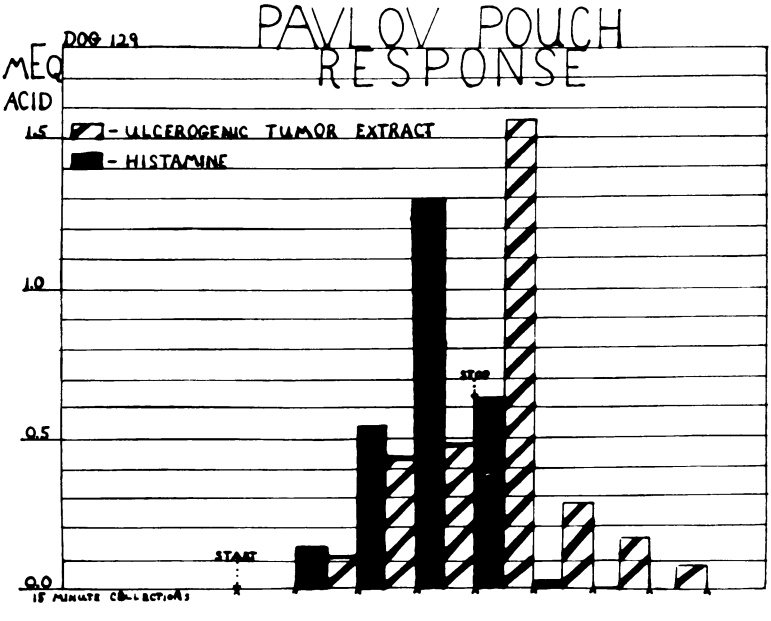

FIG. 11. Graph showing response of the tumor extract in a dog with a Pavlov pouch. Note that the acid response is more marked and longer sustained than with histamine.

much greater than that with histamine. Indeed, even the supernatant elicited a response 40 per cent as great as that of histamine! The precise material could not be identified.

Since the last operation the patient has remained essentially asymptomatic and has gained approximately 20 pounds. He has received regular injections of vitamin B_{12}. His hemogram has remained normal. He now works actively as a butcher in a local meat market and has married since his last operation.

Comment

The case presented exemplifies rather classically the severe and almost incredible ulcer diathesis associated with this syndrome. In this patient as in some reported by others multiple conventional procedures proved ineffective, nothing less than total gastric resection being efficacious in eliminating acid hypersecretion and resultant repeated ulcer formation. Furthermore, he eventually has demonstrated multiple metastatic peripancreatic tumors although histologically none have exhibited the usual criteria of malignant neoplasms. Extracts of this patient's secondary tumors do, however, contain a potent stimulus for gastric acid secretion in experimental animals with Pavlov pouches but the precise factor involved remains obscure. This is believed to be the youngest patient with this syndrome thus far reported.

Conclusion

Ulcerogenic tumors of the pancreas have been briefly reviewed and discussed. A case demonstrating this syndrome with the rather classical picture of intractable peptic ulcer formation with repeated severe hemorrhages has been presented.

Acknowledgment

We acknowledge the invaluable advice of Dr. Robert Zollinger of Ohio State University and his associates and thank them for their laboratory studies of the tumor; we thank Dr. William Patterson, formerly of the Department of Pathology, Norfolk General Hospital, for his constant assistance and also Drs. Carl Wisoff and Donald Chambers of the Department of Radiology, Norfolk General Hospital, for their advice and preparation of the x-ray photographs.

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Discussion

Dr. William A. Altemeier (Cincinnati): I believe these three papers signify a current and significant interest in malignant diseases of the pancreas. From a moderate experience, I would like to discuss Dr. Singleton's paper, in particular, and to emphasize several points which we have encountered.

First of all, I believe that the surgeon should be convinced before operation that an islet cell insulin-producing tumor does exist; this will then commit him to a thorough search and a thorough mobilization of the pancreas in an effort to demonstrate and remove this tumor.

If the surgeon is convinced of its presence beforehand, he will not schedule any other case that morning. He will take the necessary time for exploration, whether it be one hour or six or seven hours, before he has found the tumor.

I would also like to emphasize that most of these patients we have seen have had marked