Origin of the Ulcerogenic Hormone in Endocrine Induced Ulcer *

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SEVEN YEARS AGO the suggestion was made that a small adenoma of the pancreatic islets could produce tremendous gastric hypersecretion and an intractable ulcer diathesis.[12] Since then the association of a non-beta cell tumor of the pancreas with intractable ulcer and/or severe enteritis has been recognized in at least 132 cases. The original postulation that these tumors produced an ulcerogenic hormone has been verified by Gregory,[5] who extracted a potent gastrin-like hormone from non-beta islet cell tumors and their metastases. Sufficient time has now elapsed to warrant a progress report based on both clinical and experimental observations of the ulcerogenic potential of the non-beta islet cell tumors of the pancreas.

One hundred and thirty-two cases have been collected, which support the idea that a non-beta cell tumor of the pancreas has an ulcer potential in at least 90 per cent of the cases. Of these cases, 101 were reported in the literature.[10, 11, 13-82] Ten were from our own service and 21 others were described by personal communication.[83-103] Priest and Alexander, in 1957, called attention to the significance of an associated enteritis.[10] It occurs in one-third of these patients with ulcer, and is the only symptom in 10 per cent of the recorded cases. The enteritis may be so severe as to lead to the death of the patient from hypokalemia. Whether this enteritis is caused by the marked gastric hypersecretion rich in hydrochloric acid, or by a specific hormonal effect on the mucosa of the small intestine remains to be proven. A primary ulcer of the jejunum in the unusual location just beyond the ligament of Treitz was encountered in 33 patients, or 25 per cent of these cases. Perforation of such an ulcer occurred 36 times. In addition to the clinical syndrome there has been great research interest in the hormonal activities of these tumors.

The most successful extraction technics have been applied to the ulcerogenic tumor by Gregory *et al.* and subsequently by Code *et al.* Using the method of Gregory,[5] we have extracted five tumors and two metastases. These extracts have been bioassayed, using the Pavlov pouch of the dog. Figure 1 shows the typical curve of acid production from the Pavlov pouch when these extracts have been administered intravenously in the dog. The curve of acid production is quite similar to the curve produced by the extracts of gastrin prepared from the mucosa of the antrum. The fasting blood sugar must be normal throughout these experiments to avoid an acid response due to hypoglycemia. The presence of this hormone in the metastasis emphasizes the need for the removal of all acid-secreting surface by total gastrectomy, lest an early recurrence take place. This is essential even though the primary tumor is removed, since 62 per cent are malignant. Although this evidence gives strong support to the hormone activity of the non-beta cell tumor of the pancreas, others have

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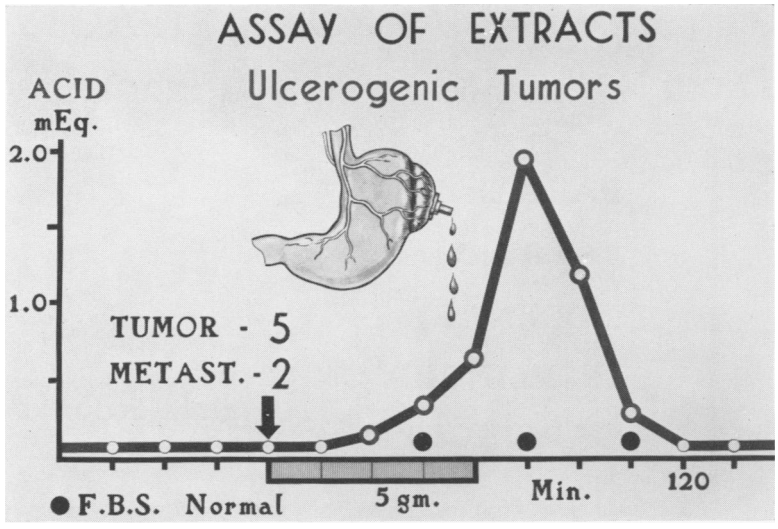

FIG. 1. The acid response in mEq. of the Pavlov pouch to extracts of the non-beta cell adenoma of the pancreas—5 tumors and 2 metastases. Blood sugars remain normal during the production of acid.

emphasized the frequent occurrence of polyglandular involvement in association with intractable ulcer.[11]

In 33 cases (25%), one or more glands of internal secretion in addition to the non-beta islet cell tumor of the pancreas were involved. The most common of these was the parathyroid, 16; followed by the adrenal, 13; pituitary, nine; insulin-producing adenomas, nine; and thyroid, eight. There was a definite familial tendency in 15 of these cases.

In an effort to determine the presence of a gastric secretagogue in these various endocrine adenomas, extracts were prepared and bio-assayed. Adenomas of the parathyroid, thyroid, adrenal (cortical adenoma and pheochromocytoma), beta-cell adenomas of the pancreas, as well as a carcinoid tumor, failed to elicit acid from the Pavlov pouch (Fig. 2). Only the extract of the non-beta cell adenoma of the pancreas contained a gastric secretagogue. The exact chemical nature of the hormone and its cellular source remain unknown.

Microscopically, the pancreatic islet tumors included in this series have an endocrine appearance histologically. Despite many efforts, these tumors do not regularly accept any of the special stains for Beta, Alpha, or Delta cells. Therefore, their islet cell of origin remains unknown. The cells are arranged in ribbons not unlike carcinoid tumors. Furthermore, the rosette arrangement of the tumor cells about a blood vessel is consistent with endocrine activity.

Although considerable significance has been ascribed to endocrine adenomas and ulcer, an increased incidence of ulcer is also recorded in association with certain chronic inflammatory lesions of the pancreas. A 15 per cent incidence in association with chronic pancreatitis has been reported.[8] An even higher incidence of ulcer has been recorded in cystic fibrosis of the pancreas, especially in the older survivors.[1,6] These clinical observations, combined with the experimental findings of marked gastric hypersecretion which follows experimentally induced acinar atrophy[2] and fibrosis, suggest the presence of a gastric secretagogue hormone in the chronically damaged pancreas as well as in the ulcerogenic tumor. Evidence to support this concept in the chronically damaged non-tumor containing pancreas can be illustrated by the following case.

Case Report

A 46-year-old hotel manager was referred to The University Hospital on January 25, 1962, complaining of severe left upper quadrant ab-

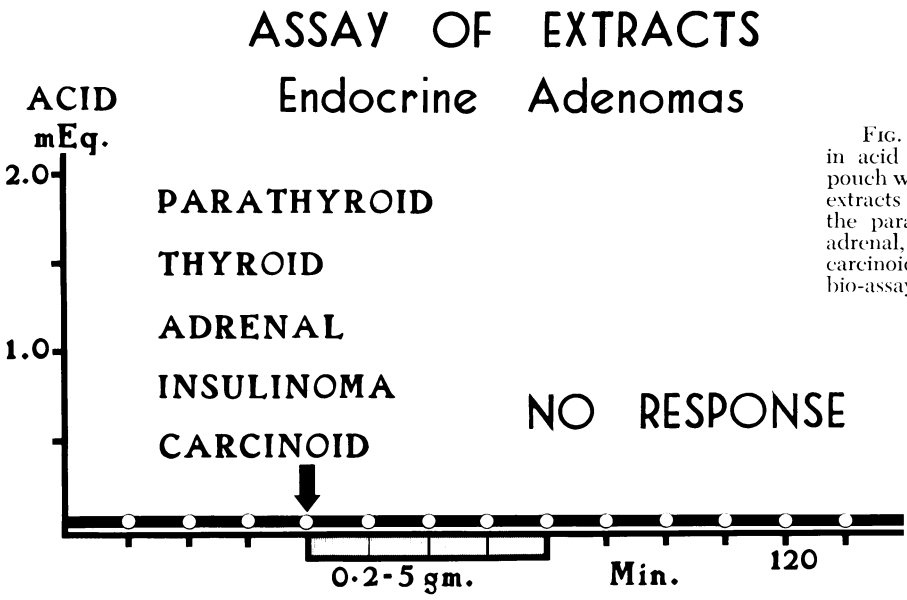

FIG. 2. No response in acid from the Pavlov pouch was obtained when extracts of adenomas of the parathyroid, thyroid, adrenal, insulinoma and carcinoid tumor, were bio-assayed.

dominal pain, partially relieved by milk and anti-acids. He was six feet tall and weighed 99 pounds. He had been in good health until 1946, when abdominal pain led him to seek medical help, and calcifications were identified by x-rays in his pancreas. For a time he took pancreatic enzymes and later he was found to have mild diabetes for which tolbutamide was given.

Approximately four years before this admission to the hospital he developed persistent symptoms of a duodenal ulcer, and his weight fell below his customary 120 pounds. In March, 1958, a subtotal gastric resection of the Billroth II type was performed. Within two weeks his ulcer symptoms recurred and persisted. In October, 1961, a marginal ulcer was demonstrated, and a bilateral vagotomy was performed with removal of additional stomach and a new anastomosis of the Billroth II type. Almost as soon as he was released from the hospital the ulcer symptoms recurred and persisted to the present admission. He was referred for study with a diagnosis of possible ulcerogenic tumor of the pancreas.

On physical examination he was found to be emaciated with several surgical scars in the upper abdomen. An upper gastro-intestinal barium study disclosed a very small residual gastric pouch, and a huge marginal ulcer, as well as calcifications scattered through the body and tail of the pancreas. Serum calcium was normal, mild diabetes

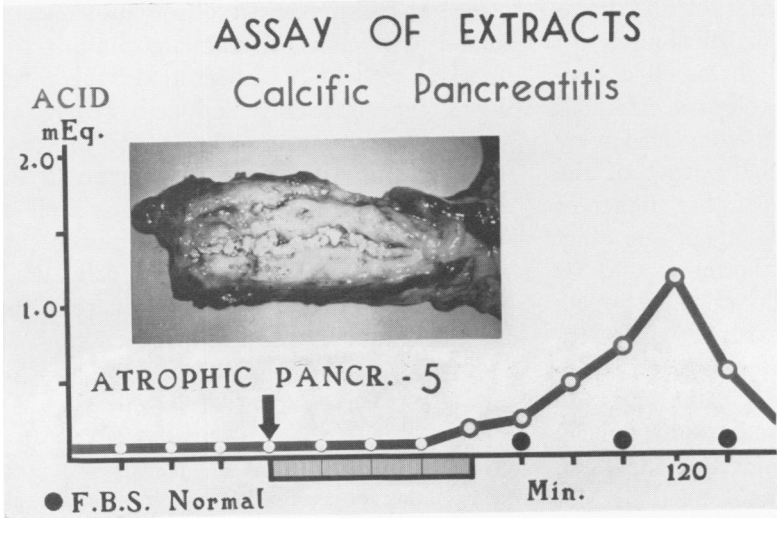

FIG. 3. Insert of gross specimen of calcific pancreatitis of patient reported. Acid response in mEq. of the Pavlov pouch to extracts of atrophic pancreas in five different patients is shown here. Fasting blood sugar remained normal during the acid response.

was present, urinary steroids were within normal limits, and x-ray of the sells turcica was normal. A 12-hour overnight gastric aspiration yielded 840 cc. containing 43 mEq. of free acid, for a total output of 32 mEq. overnight in 12 hours. A Hollander test for intact vagi was questionably positive.

On February 2, 1962, the patient was explored and no intact vagi could be found. There was no residual antrum at the old site of closure of the duodenal stump. A huge marginal ulcer extended the full width of the gastrojejunal anastomosis. The markedly atrophic pancreas filled with calculi was thoroughly mobilized and examined for the presence of a tumor, but none could be found. The body and tail of the pancreas were resected in a search for evidence of an ulcerogenic tumor. The remaining pancreatic duct was cleared of calculi and free communication with the duodenum was proven by a pancreatogram. The distal end of the pancreas was closed primarily. To control the severe ulcer diathesis a total gastrectomy was performed, using a Roux-en-Y loop of jejunum for an esophagojejunostomy in reconstruction. His postoperative course was satisfactory, and three months after surgery he is completely free of ulcer symptoms with a weight gain of five pounds.

Figure 3 shows the body and tail of the pancreas which were removed from this patient. There was no evidence of tumor. The major pancreatic duct was filled with calculi and the normal texture of the gland was replaced by a tough glistening mass of scar tissue. The curve shown is the acid response from the Pavlov pouch following the injection of an extract made from 16 grams of this atrophic pancreas. This curve, while not as marked, is similar to that produced by an extract from non-beta islet cell tumors of the pancreas. This response from atrophic pancreas has been verified in five patients. Extracts of normal human and animal pancreas show no acid response by bio-assay. However, there is an acid response to extracts of pooled atrophic dog pancreas obtained by ligation of all the pancreatic ducts.

Figure 4 shows an insert of the microscopic appearance of this patient's pancreas. The acini have been completely destroyed and replaced by scar tissue. There has been a tremendous hyperplasia and proliferation of islet tissue. Conglomerate groups of islets are abnormally large and are found *back-to-back* with islet proliferation from small ductules. This predomi-

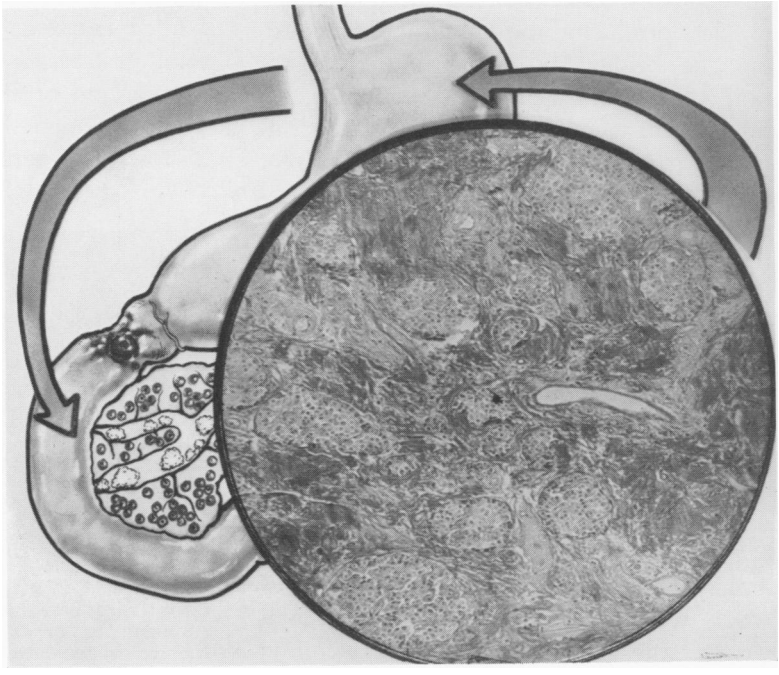

FIG. 4. An insert of a microscopic section of the atrophic pancreas of the patient reported shows marked islet hyperplasia and proliferation. This predominance of islets initiates the vicious circle of acid hypersecretion which causes the release of secretin which in turn stimulates the pancreas.

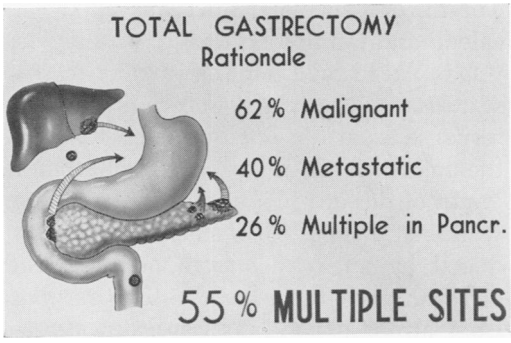

FIG. 5. In 55 per cent of the cases reported, multiple sites for the potential production of the gastric secretagogue were found. This percentage corresponds closely to the incidence of recurrence following local excision of an obvious tumor of the pancreas. This finding constitutes the rationale for treatment with total gastrectomy.

nance of islets in chronic pancreatitis has been described by Horgan[7] and Friedlander.[3] It might be concluded that the predominance of islet tissue in the atrophic pancreas produces a gastric secretagogue, as does the non-beta cell tumor.

The presence of excessive amounts of a gastric secretagogue in chronic pancreatitis may well play a major role in setting up a vicious circle (Fig. 4), which has long challenged the clinician. The predominance of islets producing the potent gastric secretagogue brings about gastric hypersecretion, which in turn produces secretin in the duodenum, which in turn is a potent pancreatic stimulant. This constant indirect hormonal stimulation of the diseased pancreas overrides the clinician's best efforts to keep the gland at physiologic rest. Therefore, the chronically inflamed pancreas may be its own worst enemy! To break the vicious circle, the clinician may have to remove either the pancreas or the stomach, but if possible he should carry out a more conservative procedure which allows free drainage and repair of the acini of the damaged pancreas.[9]

While the gastric secretagogue from the pancreas may be controlled in a variety of ways, we continue to believe that total gastrectomy is the best way of controlling the fulminating ulcer diathesis associated with non-beta islet cell tumors of the pancreas. This radical approach is supported by the fact that 62 per cent of these non-beta islet cell tumors are malignant and 40 per cent have metastases, which also produce the gastric secretagogue. In 26 per cent, the tumors are multiple throughout the pancreas. Therefore, it is important to remember that in 55 per cent of the cases there are multiple sites for the potential production of this potent gastric secretagogue (Fig. 5). These statistics would predict recurrent ulceration in more than half of the cases if any acid-secreting surface of the stomach was allowed to remain. This prediction is borne out by the clinical reports (Fig. 6). For example, the two general types of conservative treatment have been local removal of the tumor with a recurrence rate of 60 per cent, and radical gastric resection combined with partial removal of the pancreas with a recurrence rate of 57 per cent. In contrast, there were no recurrences following the total gastrectomy, which is consistent with the old adage, *no acid, no ulcer!* The mortality was quite similar in all three approaches and ranged between 12.5 and 16 per cent. If total gastrectomy would be required following one of the more conservative approaches, then the combined mortality of 25 to 30 per cent might be anticipated. It

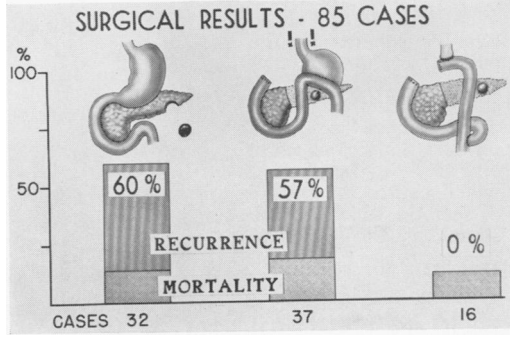

FIG. 6. The surgical results of the three major operative approaches to the treatment of the ulcerogenic tumor of the pancreas are shown with the recurrence rate and mortality.

is impossible at present to give an accurate long-term follow up as to the true incidence of recurrence following the more conservative procedures.

In contrast to most patients with carcinoma of the stomach, these patients do surprisingly well following total gastrectomy. One of the original patients reported in 1955, who was treated by total gastrectomy and removal of lymph nodes containing metastic non-beta islet cell tumors on the surface of the pancreas, has maintained her weight above ideal. The slow growth of these tumors has been emphasized by others.[4] This patient was delivered of a five and one-half pound baby girl in February, 1962, seven and one-half years following total gastrectomy, clearly demonstrating that normal life is possible following total gastrectomy.

Conclusions

1. The concept that non-beta islet cell tumors of the pancreas are associated with intractable ulcer and/or enteritis is supported by 132 cases.

2. Severe enteritis occurred with ulcer in 30 per cent of the patients and was the only symptom in 10 per cent.

3. Perforation of a primary jejunal ulcer just beyond the ligament of Treitz occurred 36 times.

4. Using the method of Gregory, a potent gastrin-like hormone was confirmed by bio-assay of the extracts of five islet cell tumors and two metastases.

5. Polyglandular involvement including one or more glands of internal secretion, in addition to the non-beta islet cell tumor, occurred in 25 per cent of the cases.

6. Adenomas of the parathyroid, thyroid, adrenal, beta cell adenomas of the pancreas, as well as carcinoid tumor, failed to demonstrate the presence of a gastric secretagogue by bio-assay.

7. The islet cell of origin of these tumors remains obscure and further study is indicated.

8. The increased incidence of ulcer associated with certain inflammatory diseases of the pancreas suggests the presence of a gastric secretagogue in the chronically damaged pancreas as well as in the ulcerogenic tumor.

9. Bio-assay of the atrophied pancreas from patients, as well as the atrophy in dogs which follows ductal ligation, showed the presence of a gastric secretagogue.

10. The gastric secretagogue produced when hyperplasia and proliferation of islet tissue are present in the atrophic pancreas may play a major rule in setting up the vicious circle which defies the clinician's effort to place the pancreas at rest. Any planned surgical procedure should allow for free drainage and repair of the acini of the damaged pancreas.

11. In 55 per cent of the reported cases of non-beta cell tumor of the pancreas, multiple sites for the potential production of the gastric secretagogue were found. This percentage corresponds closely with the incidence of recurrence following local excision of an obvious tumor of the pancreas or subtotal gastric resection combined with hemi-pancreatectomy.

12. Total gastrectomy remains the treatment of choice in the management of the ulcerogenic tumor of the pancreas.

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83–103. 21 Cases reported by personal communication.

Discussion

Dr. John H. Mulholland (New York): It is a pleasure to discuss this paper and to have read the manuscript beforehand, even though I am at a disadvantage following the usual professional presentation we have come to expect of Dr. Zollinger.

This is one more item of knowledge chipped from our mountain of ignorance about ulceration of the gastro-intestinal tract. Dr. Zollinger presented a great deal of material in a short time. He included, as you noted, material on the biochemistry of most complex gastro-intestinal hormones; on internal secretions of that enormous endocrinologic structure, the gastro-intestinal tract; and on human genetics.

Of particular interest was his reference to the atrophic pancreas as a source of the secretagogue which initiated a vicious cycle resulting in uleration. The precise source of the acid stimulating material was not clear to me. When pancreatic acinar cells are destroyed many potent enzymes are released, some of which have the property of denaturing of lysing proteins. Such cellular destruction ends in the atrophy which was evident in the photomicrograph he showed. I would like to ask Dr. Zollinger, does he attribute the source of secretagogue to deteriorating acinar cells or to relatively well preserved islet cells?

Dr. Edgar J. Poth (Galveston): I wish only to draw your attention to one situation which I have observed in conjunction with this over-all study, and that is, if you remove the entire pancreas and then give histamine in beeswax, you can develop fulminating peptic ulcer disease, which I think we did in 1948. This does not fit in completely with a lot of these observations and I wonder if Dr. Zollinger can comment on this observation.

Dr. Edwin H. Ellison (Milwaukee): Once again we are indebted to Dr. Zollinger and his associates for their observations on the mechanism of ulceration in the Zollinger-Ellison Syndrome and the choice of operation when faced with this problem.

I, too, agree that total gastrectomy with removal of the resectable tumor, but short of total pancreatectomy, continues to be the surgical treatment of choice, even when the presenting complaint is prolonged, persistent disabling diarrhea.

A recent personal experience will serve to emphasize our feeling that total gastrectomy still remains the treatment of choice. I. B., a 49-year-old white woman was referred to Marquette for evaluation in March of this year with a nine-year history of severe diarrhea and weighing only 81 pounds. At operation in 1956 a lesion thought to be a metastatic carcinoid of the pancreas had been removed. Two years later the slides were reviewed and the diagnosis was changed to islet cell carcinoma.

During her illness the average number of loose stools per day varied from three in 1953 to as many as 15 or more in 1962. Following excision of what later proved to be an islet cell carcinoma from the pancreas the patient had a relief of her symptoms for a period of three months. The diarrhea then recurred requiring two to three hospitalizations per year up until March of this year. Therapy had included a glutein free diet, cortisone, and pancreatin by medical consultants all to no avail.

In 1958, excision of an islet cell cancer of the liver presumably in the passages resulted in temporary improvement probably related to constant Levin suction for a considerable time after the operation. In January of this year, that is, 1962, during an admission for massive hemorrhage, a duodenal ulcer was diagnosed for the first time.