ULCEROGENIC TUMORS

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It is a great honor for me to be invited to speak before the internationally famous Japanese Society of Gastroenterological Surgery and the Japanese Society of Gastroenterology. I would like to take this opportunity to congratulate all of the distinguished speakers who preceded me on this podium.

The genius and ingenuity of the Japanese medical profession in the field of gastroenterology are well known throughout the world. Your contributions to both the medical and surgical aspects of diseases of the gastrointestinal tract have been consistent and fundamental. My colleagues in the United States were envious, indeed, of my prized invitation to join you on this occasion and learn, first hand, of your many advances in gastroenterology and gastroenterological surgery.

Today, when so much emphasis is placed on the dramatics of cardiovascular surgery, there is a tendency to overlook the significance and frequency of diseases involving the gastrointestinal tract. It is vitally important that we continue to expand our mutual research efforts and exchange ideas as rapidly as possible in order to bring comfort and ensure the productivity of literally millions of our fellow men suffering from such unresolved diseases as duodenal ulcer, ulcerative colitis, pancreatitis and cholelithiasis, to mention but a few.

These comments will be related to certain non-beta islet cell tumors of the pancreas, which have been proven capable of elaborating the first two gastrointestinal hormones, more than 60 years after their original description.

Professor Starling, in the Croonian Lecture1) to the Royal College of Physicians in 1905, first used the word Hormone to describe the action of an extract of the duodenum, designated Secretin, which he and Professor Bayliss had discovered in 19032); as well as the action of Gastrin, extracted from the antrum, which had been reported by J.S. Edkins3) one month before Starling's lecture. Starling thought that both secretin and gastrin certainly met all the requirements of a hormone, or chemical messenger: a substance which comes from one organ and is carried by the blood to another, and there causes either excitement or inhibition of that organ.

For another 50 or more years, it was not apparent to either the physiologists or clinicians that these chemical messengers could be produced outside the stomach or duodenum, or that they might be elaborated in excessive amounts by certain endocrine tumors of the pancreas. Furthermore, it was not appreciated that such excesses of either hormone could cause a recognizable clinical syndrome.

That the pancreas might play a role in the etiology of peptic ulcer, however, was not a new idea to surgical physiologists. Dr. Edgar Poth, in 1948, after a series of animal experiments in which dogs with pancreatic duct ligation or total pancreatectomy were given histamine in beeswax, wrote: BOTH THE INTERNAL AND EXTERNAL SECRETIONS OF THE PANCREAS MAY BE IMPLICATED IN ULCER FORMATION4).

The relationship between the pancreas and peptic ulcer has also been emphasized by Drs. Murata and Hirono in a presentation to the 67th Annual Congress of the Japan Surgical Society5). In their study of 687 cases of peptic ulcer, they found that the pancreas was implicated in 43, or 6.8 per cent of the total series. In this group of 43 patients were five ulcerogenic islet cell tumors, eight cases of islet hyperplasia, 13 of fibrosis and 20 of chronic pancreatitis.

Our own special interest in gastropancreatic relationships can be dated to 1947, when we treated a patient who had developed a marginal ulcer after posterior gastroenterostomy. A vagotomy was per-

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formed and a large tumor mass involving the body and tail of the pancreas was found, from which a biopsy was taken. There was considerable excitement among the surgical residents when postoperative gastric analyses showed that the acid values were not altered by the vagotomy. There is no doubt in my mind that they thought the new Professor was not adept at performing a complete vagotomy. On permanent section, the tumor was found to be malignant islet cell tumor and within 10 days, the patient was re-explored and the tumor removed. The patient promptly became achlorhydric and in her five remaining years of life, she was free of ulcer symptoms. Interestingly enough, a basophile adenoma of the pituitary gland was discovered at the time of postmortem examination.

Although this patient’s gastric acid values promptly came down and remained normal after removal of the pancreatic tumor, the true significance of this observation was not appreciated until several years later when two similar cases were encountered. It is fair to state that she was my first case of what would come to be called the Zollinger-Ellison syndrome.

Eight years later, on April 29, 1955, Dr. Ellison and I presented two problem cases of recurrent ulceration before the American Surgical Association meeting in Philadelphia. Both patients were women, one 36 and the other 19 years of age. The older patient was first seen in July 1952 by Dr. Ellison because of an eight year history of diarrhea and abdominal pain. Within 30 days she underwent two resections of large jejunal ulcers beyond the ligament of Treitz, which were followed in two months by a vagotomy and two gastric resections. As a desperate last measure, total gastrectomy was accomplished, but she succumbed to her disease less than one month later. At autopsy, a well-encapsulated 1 cm tumor nodule was found in the central portion of the pancreas. Several similarly-encapsulated nodules were found around the major adenoma.

The second, younger patient was a 19-year-old girl who had had previous closure of two perforated jejunal ulcers beyond the ligament of Treitz in 1953. These perforations were closed and her convalescence was uneventful except for the development of intestinal obstruction within nine months, which required lysis of adhesions. When first seen by us in January 1954, the patient was having severe ulcer symptoms with a 12-hour gastric acid output of 308 mEq. A portion of her fundus was removed and a radical gastric resection performed, which left a lesser curvature gastric remnant only 6 x 8 cm in size. The vagus nerves were cut and a Billroth I reconstruction established. Within nine months, she again had evidence of hypersecretion even though she had been given 2,000 r. of X-ray therapy to the gastric remnant. Finally it became necessary to remove her remaining stomach. At operation, we found a deep ulcer in the esophagus adjacent to the esophagogastric junction, and a large, penetrating ulcer at the gastroduodenal anastomosis. In addition, two small brown lymph nodes were removed from the surface of the pancreas, which were subsequently proven to contain metastatic non-beta islet cell tumor of the pancreas.

This patient is living and well today. She had two children, seven and eight years after total gastrectomy, and currently weighs 142 pounds, which is well above her ideal weight. She requires only one injection of Vitamin B-12 every month, in contrast to the expensive medications she would have required if her entire pancreas had been removed because of the metastatic tumor.

One the basis of these two cases, “an ulcerogenic humoral factor of pancreatic islet origin” was postulated, and a diagnostic triad for a new syndrome proposed, consisting of:

1. “The presence of primary peptic ulcerations 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 proportions, persisting despite adequate conventional medical, surgical or irradiation therapy.

This communication set off a chain reaction of further case reports from all over the world, and the following year, Eiseman and Maynard suggested characterizing this diagnostic triad under the name of Zollinger-Ellison syndrome.

In the 14 years that have elapsed since the original description, more than 600 cases of ulcerogenic tumor of the pancreas have been reported; and 500 of these cases have been studied in detail in the Islet
ULCEROGENIC TUMOR OF PANCREAS

500 Cases

<table>
<thead>
<tr>
<th>Ulcer Complications</th>
<th>Case %</th>
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<tbody>
<tr>
<td>Intractability</td>
<td>46</td>
</tr>
<tr>
<td>Perforation</td>
<td>17</td>
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<td>Primary Jejunal (7%)</td>
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<td>Misc.</td>
<td>1</td>
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<td>None-17%</td>
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(Fig. 1)

Cell Tumor Registry at The Ohio State University. Approximately 46 per cent of these patients had intractable ulcer pain and a free perforation occurred in 17 per cent. Of great significance is the fact that 7 per cent of the patients had a perforation which occurred in the jejunum, just beyond the ligament of Treitz (Fig. 1).

As Wermer and others have pointed out, there is a tendency for more than one gland of internal secretion to be involved with the islet cell tumor of the pancreas. This is commonly referred to as Multiple Endocrine Adenomatosis, or the MEA Syndrome, with a familial variant which is known as the Wermer Syndrome. Only one-half of the cases studied at Ohio State University had a reference to a specific search for evidence of a hyperfunctioning endocrine tumor, other than the ulcerogenic tumor of the pancreas.

The parathyroid gland was most frequently involved, with an incidence of 35 per cent, followed by the pituitary and adrenal glands which were each listed in 13 per cent of the cases. A thyroid adenoma was proven in 11 per cent of the cases, while 3 per cent were found to have a beta cell adenoma and 2 per cent had carcinoid tumors of the gastrointestinal tract. It is impossible to accurately determine the true incidence of hyperparathyroidism, but the association is sufficiently common to make it necessary that every patient with an ulcerogenic tumor be thoroughly evaluated by means of the appropriate blood studies and by X-rays of the skeletal system.

The problem of establishing the presence of an ulcerogenic tumor preoperatively can present a real challenge to the surgeon. The diagnosis should be suspected if a patient produces 100 ml of gastric juice per hour from an unobstructed stomach, or very soon after a radical gastric resection, which may have included vagotomy. Of even greater significance, according to Ruppert and his colleagues, is the ratio of basal to stimulated concentration of acid following the administration of histamine. Although the volume or output of gastric juice may vary tremendously, there is relatively little change in the concentration of hydrochloric acid per liter per hour after maximum histamine stimulation; and a ratio of 0.6 or greater is considered suggestive of a gastrin-producing ulcerogenic tumor.

Roentgenologists should be able to recognize several features of this syndrome which result from the massive gastric hypersecretion. According to Nelson and Christoforidis, the important diagnostic signs are markedly hypertrophic gastric rugae and the presence of large amounts of gastric fluid despite fasting and the lack of any obstruction. A primary jejunal ulcer beyond the ligament of Treitz, as occurred in our first two cases, is still considered pathognomonic of the ulcerogenic syndrome; however, the peptic ulcerations usually occur in the duodenum. Recurrent ulcers following a gastric resection tend to be located along the mesenteric border in the efferent loop, rather than in the usual marginal location.

Within five years of the original description of the ulcerogenic syndrome, Professor R.A. Gregory and his colleague, Hilda Tracy, demonstrated the hormonal nature of the gastric secretagogue by extracting from one of the tumors a substance having the same effect on gastric secretion as gastrin extracted by the same method from hog antral mucosa. They also obtained several small metastatic liver nodules which were found to contain 35 times more gastrin activity than an equal amount of hog antrum. These demonstrations renewed interest in the mechanisms of gastric hypersecretion and methods for its control, as well as leading to the development of additional diagnostic tests for the ulcerogenic tumor.

Confirmation of the presence of an ulcerogenic tumor can often be obtained by a search for excessive-
GASTRIN RADIOIMMUNOASSAY

McGuigan

Amounts of tumor-produced gastric secretagogue in specimens of early morning, fasting serum, urine or gastric juice. We have employed the bioassay method of Lai to provide diagnostic verification of an ulcerogenic tumor. The technique consists of administering intravenously 10 ml of the patient's serum, gastric juice or urine to an anesthetized male Wistar rat, having an isolated stomach through which saline can be perfused. After a baseline of acid secretion has been established, the animal's stomach is stimulated with porcine gastrin. When the baseline is re-established following the infusion of saline, the test sample is infused. In the presence of an ulcerogenic tumor, there is usually a prompt, double-the-baseline response in the output of acid from the animal's stomach. It has been our experience that a fair degree of accuracy is achieved if the acid-output curves can be replicated in at least two viable animals, which have consistently responded throughout the two to three hour test.

It is hoped that immunochemical measurement of serum levels of gastrin, using the radioimmunoassay technique of Dr. James McGuigan, will afford a direct and accurate method for the diagnosis of ulcerogenic tumors of the pancreas. This assay is a double-antibody test in which the gastrin in a patient's serum is in competition for binding sites on a gastrin antibody molecule, which has been made in rabbits. The serum to be tested is first mixed with a known quantity of rabbit gastrin antibody and then synthetic gastrin, which has been labeled with Iodine-131, is added to the solution. If there is an excessive amount of gastrin in the patient's serum to react with the rabbit antibody, very little of the radiolabeled gastrin will find a rabbit gastrin antibody molecule with which to bind.

The second antibody, one against rabbit globulin, is next added to the solution containing serum gastrin, rabbit antibody against gastrin and radiolabeled synthetic gastrin; and a precipitate is created. A ratio between the number of counts of radioactivity in the precipitate and the number of counts in the supernate is obtained.

If the number of counts in the precipitate is high, the amount of circulating gastrin in the patient's serum is low. If there are very few radioactive counts in the precipitate, there is a great deal of gastrin in the patient's serum. Picogram levels of gastrin are assigned to the radioactivity which remains after the counting.

In an early report, serum gastrin levels in four patients with an ulcerogenic tumor exceeded by almost tenfold the mean serum gastrin level of 425 picograms/ml in the control group. Determinations in a greater number of cases, however, have reduced the level to 200 picograms/ml as the lower limit of the ulcerogenic tumor range. Wider clinical application of the immunoassay should allow accurate diagnosis of the ulcerogenic tumor, and more clearly define the necessity of total gastrectomy, particularly when all other evidence is in the gray or doubtful zone.

Determining the existence of an ulcerogenic tumor at the time of operation many times is difficult. If gross tumor is found in the pancreas or if there is evidence of metastases, the surgeon is reassured to proceed with total gastrectomy. However, difficulty arises when no tumor can be found, but the clinical and laboratory evidence strongly favors an ulcerogenic tumor. The finding of an ulcer in the jejunum...
beyond the ligament of Treitz is a very significant finding. We have observed one patient who had three perforations in this area. At the time of the third operation, an adenoma was found on microscopic examination of the resected first portion of the duodenum.

The ulcerogenic tumor may be so small as to escape thorough palpation of the head, body and tail of the pancreas, even after extensive mobilization of these structures. Adjacent lymph nodes should be excised and sent to the pathologist for frozen section examination. Failing to find evidence of tumor, the surgeon is justified in removing the tail and left side of the body of the pancreas to permit microscopic search for evidence of microadenomatosi. An unexplained source of a gastric secretagogue is nesidioblastosis, a state in which there is a proliferation of islet cells, particularly in the presence of extensive pancreatitis. While this source has been debated, Elliott and his co-workers found positive evidence of such in a small number of cases of chronic calcific pancreatitis associated with severe ulcer diathesis.

The characteristics of the ulcerogenic tumor make removal of all acid-secreting surface by total gastrectomy the logical surgical procedure. The tendency for these patients to have multiple foci for the production of gastrin is explained by the fact that the tumors are multiple in 75 per cent of the cases, malignant in 61 per cent and there is evidence of metastases in 44 per cent. A review of the available cases suggests an actual recurrence rate of about 57 per cent if any acid-secreting surface remains. Total removal of the stomach may also inhibit further growth of the tumor or its metastases, according to Dr. Stanley Friesen, but this remains to be proven.

Although present in one of the original cases, diarrhea was not included in the diagnostic triad of the ulcerogenic syndrome. For some time, then, it was believed that the diarrhea in every case was due to the marked gastric hypersecretion, which resulted in neutralization of the pancreatic enzymes as well as irrigation of the gastrointestinal mucosa. However, within two years of the initial report, clinicians began to question whether this was an adequate explanation for the diarrhea in all cases. The demonstration by Gregory that gastrin is the active principle in the ulcerogenic tumor provided a sound explanation for the production of diarrhea on the basis of a direct stimulatory effect of the hormone on the gastrointestinal tract.

With almost 600 cases now reported, it has become possible to sort the diarrhea patients into three groups. Approximately 30 per cent of them have gastric hypersecretion, diarrhea, and peptic ulceration, while 6 per cent have gastric hypersecretion and diarrhea but no peptic ulceration. In both types of cases, gastrin activity has been extracted from the non-beta islet cell tumors. The third and smallest group, numbering approximately 27, have an unusual and exciting entity which will now be discussed in some detail.

For several years, after the reports of Priest and Alexander and Verner and Morrison, we were challenged to explain these unusual patients with a non-beta islet cell tumor who did not have hypersecretion or ulcer, but rather a fulminating watery diarrhea which led to marked potassium loss and death from hypokalemic nephropathy. Murray and his colleagues in 1961 reported achlorhydria for the first time in a patient with a non-beta islet cell tumor and watery diarrhea. The previous impressions that hypersecretion and hyperacidity were absent in such patients were thereby confirmed, and the acid factor was invalidated as the mechanism of the diarrhea. This diarrheal entity, clearly established as not a variant of the Zollinger-Ellison syndrome, was called “Pancreatic Cholera” by Matsumoto in 1966, and later the WDHA (Watery Diarrhea-Hypokalemia-Achlorhydria) syndrome by Marks and his associates.

A recent study of two such patients at our Clinic has suggested that these diarrheogenic tumors produce a secretin-like hormone. These patients, both married women, 24 and 47 years of age, presented with the classical feature of fulminating watery diarrhea, which approximated 2 to 4 liters a day. The younger patient had had cyclical diarrhea over a four-year period, while the second patient had a 9-month history of constant diarrhea. Both patients had a tremendous loss of potassium in the stool, which resulted in severe hypokalemia; the serum potassium levels were consistently less than 3 mEq/L, even with the administration of 200 mEq of potassium every 24 hours. In both cases, the absence of free hydrochloric acid was demonstrated by gastric analysis, and Lai rat serum bioassays were negative for circulating gastrin.

At operation, the younger patient was found to have a large, discrete islet cell tumor in the midportion
of the pancreas, as well as a smaller tumor in the tail and diffuse microadenomatosis. The body and tail of the pancreas were removed. The older patient had evidence of hepatic metastases and succumbed to her disease within 30 days of operation. At post-mortem examination, there was a small non-beta islet cell tumor found deep in the head of the pancreas.

Three significant findings led eventually to our supposition that these islet cell tumors were elaborating a secretin-like hormone. During the operation on the younger patient, it was observed that the duodenum appeared to refil with secretions and the gallbladder was greatly distended. Enough bile was aspirated from the huge gallbladder for complete chemical analysis, as part of a study on the etiology of cholesterol gallstones.

The second indication of secretin-like activity became apparent within five days after operation on the younger patient. Numerous gastric analyses performed before surgery had demonstrated basal achlorhydria which could be overridden by the administration of histamine. Five days after operation, with nothing having been done to the stomach, gastric analysis, without histamine stimulation, showed the presence of 55 mEq/L of free hydrochloric acid. This suggested that a gastric acid inhibitor had been removed with the tumor. Followup studies as long as 8-1/2 months later have continued to show the presence of free hydrochloric acid. It was established by the work of Dragstedt and others that secretin will inhibit the production of hydrochloric acid, but that this inhibition can be overcome by the administration of histamine27).

The third clue to secretin activity came with the unexpected finding on chemical analysis of the bile of high chloride and bicarbonate levels in the otherwise very dilute bile. A review of the choleretic hormones disclosed that only secretin infusions in animals were associated with the significantly elevated levels of both chloride and bicarbonate in bile28).

Two of these observations—the dilated gallbladder and the secretin-like choleresis—were confirmed in the second case, several months later. Postoperative gastric analyses could not be performed in the second patient, however, because of the extensive metastatic tumor involvement which caused her early demise.

With this presumptive evidence pointing to a secretin-like hormone of islet cell origin, hydrochloric acid extracts of the tumors were prepared for intravenous injection using a method provided by Dr. T.M. Lin of the Eli Lilly Laboratories29). Mongrel dogs with the pylorus and cystic duct ligated and the pancreatic duct and common bile duct ligated were used as test animals. After the induction of phenobarbital anesthesia, pure natural (Jorpes) and synthetic secretion (Bodanszky) were injected in amounts of 25 units to establish the typical pancreatic response for comparison with the tumor extracts. The volume and bicarbonate responses of the extract made from the metastasis of the older patient paralleled that of the natural and synthetic secretion, with a positive response obtained in five different animals. No response could be obtained from extracts of the firm, smaller tumor removed from the younger patient.

Dr. Kraft and his co-workers recently reviewed the available world literature in an effort to evaluate the major clinical and laboratory findings of the diarrheogenic syndrome30). The case descriptions of 27 patients with this syndrome were found in the literature, one of which was the excellent report of Dr. Umeyama and his colleagues entitled “Case of Non-Functioning Cancer of the Islands of Langerhans with Chronic Diarrhea as the Chief Complaint”31).

In the 20 cases with reported measurements, the average daily stool volume during acute diarrheal episodes was 6 liters with a stool potassium loss of 350 mEq/day, in contrast to the normal fecal potassium excretion of 13 mEq/day. The serum potassium level in 23 patients averaged 2.2 mEq/L during the episodes of diarrhea. Despite aggressive fluid and electrolyte replacement, stable correction was achieved only after spontaneous remission of the diarrhea, excision of the tumor or therapy with steroids.

We were impressed by the incidence of associated hypercalcemia, which is much higher in this group of patients than is seen with an ulcerogenic tumor. Serum calcium levels were measured in 21 of the 27 reported cases, and a total of 16 had elevated levels—one-half of which were greater than 12 mg%. The hypercalcemia was not altered in two patients having removal of a parathyroid adenoma.

One of our patients had recurrent hypercalcemia after removal of 3-1/2 hyperplastic parathyroid glands, and underwent a second exploration of the neck and mediastinum, but no parathyroid tissue was
FIRST GI HORMONES

Clinical Syndrome
Secretin-1902
(Duodenum)
Bayliss & Starling
Gastrin-1905
(Antrum)
Edkins
Islet Cell Tumor Origin
Diarrheogenic-1968
Ulcerogenic-1955

found. It was later determined that elevations in her serum calcium were directly related to the severity of the diarrhea, and after removal of her pancreatic tumor, this patient has remained normocalcemic.

In view of the recognized hormone multipotential of islet cell tumors, the ectopic production of parathormone or a parathormone-like substance is considered a very strong possibility, but bioassays and immunoassays of such tumors will be necessary to prove this supposition. We would suggest, however, that in suspected cases of diarrheogenic tumor, there is no indication to proceed with parathyroid surgery before the pancreas is explored.

The diarrheogenic syndrome, then, should be suspected in patients with watery diarrhea amounting to 6 liters or more per day, and serum potassium levels of slightly greater than 2 mEq/L. The diagnosis is further confirmed if there is an absence or very low values of free hydrochloric acid by gastric analysis. Blood levels of calcium and sugar are commonly elevated in such patients. In 27 reported cases, surgical excision was possible in approximately half of the patients. In the presence of metastatic disease, steroid therapy may be utilized in an attempt to control the fulminating watery diarrhea. More recently, the drug, Streptozotocin, in dosages of 3 grams/meter$^2$, has been reported to be effective in treating a few patients with islet cell tumors of the pancreas; but this remains an experimental drug$^{32}$.

Summary

It seems reasonable to assume that non-beta islet cell tumors of the pancreas can elaborate secretin as well as gastrin, since they share a common cell of origin with the antrum and the duodenum where these hormones are normally produced.

Tumors of the pancreas are known to produce a wide variety of humoral substances, and it seems likely that they are synthesized by pluripotential cells contained in the pancreas. The beta cell has been identified as the site of production of insulin, while the alpha cell has been shown to produce glucagon. The cell responsible for the production of gastrin, secretin, ACTH and MSH$^{33}$ has not been specifically identified, despite intensive light- and electron-microscopic studies. A few tumors arising from the pancreas have been found to elaborate serotonin, and perhaps the enterochromaffin cell is responsible$^{34}$. The future may well unfold even more hormones being produced by endocrine tumors of islet cell origin.

The impact of the diarrheogenic tumor has been to establish another clinical syndrome, characterized by watery diarrhea, hypokalemia and achlorhydria (Fig. 3). Clinical and laboratory evidence supports the concept that secretin, to which the name “hormone” was first applied, is the active principle in this syndrome. It has stimulated further studies of gastrointestinal absorption, and also confirmed the hormone multipotential of islet cell tumors, perhaps on the basis of their embryological origin.

The ulcerogenic tumor, on the other hand, has explained some surgical failures which in the past may have condemned certain standard operations employed in the treatment of duodenal ulcer. It has tended to renew interest in upper gastrointestinal physiology and has stimulated studies of gastrin. The ulcerogenic tumor has also increased the hormonal scope of the pancreas, and established a clinical syndrome on the basis of almost 600 reported cases. The studies it has initiated may well play a role in the development of new methods of treating ulcers, utilizing immunological methods to control gastric hypersecretion.
Conclusions

Two distinct clinical syndromes are now associated with non-beta islet cell tumors of the pancreas. The ulcerogenic syndrome, described in 1955, consists of massive gastric hypersecretion, a fulminating ulcer diathesis and a non-beta islet cell tumor of the pancreas which has been shown to elaborate the hormone gastrin. More recently, the diarrheogenic syndrome has been reported. This disease entity—consisting of watery diarrhea, hypokalemia, achlorhydria, a high incidence of hypercalcemia and less frequently, hyperglycemia—is felt to result from islet cell tumor production of the hormone, secretin. More than 60 years after their original description, the first two gastrointestinal hormones, gastrin and secretin, have been implicated in clinical syndromes caused by non-beta islet cell tumors of the pancreas.

References

8) Unpublished Data, R.M. Zollinger, M.D.: The Ohio State University Islet Cell Tumor Registry.


